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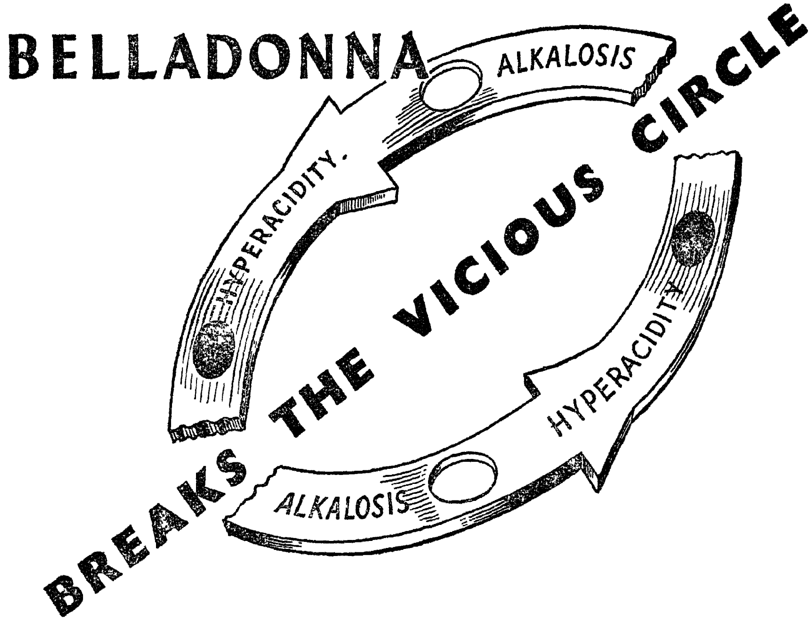

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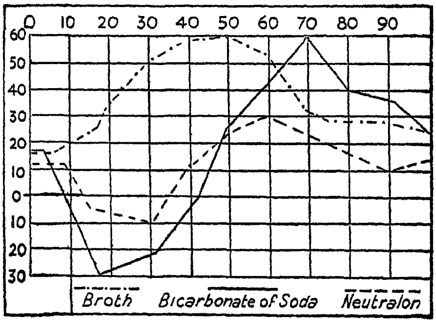

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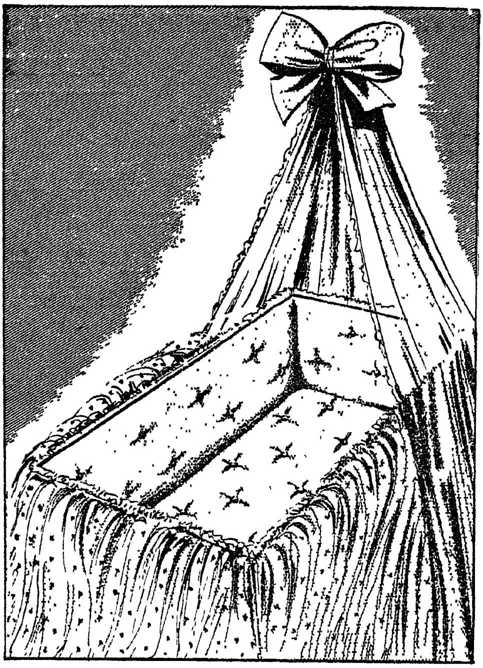

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REGIONAL COSTAL PERIOSTITIS

PRELIMINARY OBSERVATIONS ON A NEGLECTED ENTITY

R. J. Vakil *

It was whilst engaged in investigating the causes of chest pain that my attention was first directed by an observant patient to the existence of this interesting clinical entity.

At the First Annual Conference of the Association of Physicians of India, I[6] drew the attention of the medical profession to the existence of this entity, for which I proposed the alternative designations of "Costal Periostitis" and "Regional Costal Periostitis".

Since that time, many more cases of this sort have been brought to my notice by friends and colleagues; as a result, I am now in a position to present a fairly comprehensive clinical picture of the condition.

A routine check-up of the medical literature for any mention or reference to this condition in the past has proved disappointing. In 1940, Staehlin[5] of Basel, in an interesting paper on Affections of Costal Cartilages, has described so-called "inexplicable foci of tenderness and pain" in the course of "inflammatory lesions" of the costal cartilages; in the same paper, he also reports a few cases of so-called "isolated rheumatic perichondritis."

A TYPICAL CASE REPORT.

The following case notes from a typical case will serve to introduce the clinical concept of Regional Costal Periostitis better than any theoretical discussion.

Case No. 22.

A Parsee married woman, aged 38 years, was first seen in March 1947 for a "dull aching" pain in the upper part of the anterior wall of the left chest, of three months' duration.

Besides being of a nervous disposition at all times she had gone through a phase of "nervous breakdown" in 1939, after which she had been the subject of vague, "rheumatic-like" pains and aches in various joints and muscles of the body.

---

* From the Department of Medicine, K. E. M. Hospital, Bombay.

The chest-pain was accurately localized by the patient at the site of the small fusiform enlargement over the third left rib. The pain was described as being continuous, although with short remissions and exacerbations, worse in the morning and "after a day of exertion", and worse on cold and chilly days. There was no relation to food or exertion, no radiation of the pain in any direction and no accompanying sensations of constriction or angor animi.

Over the anterior aspect of the third rib, a fusiform and tender enlargement, about an inch in diameter and with no superjacent redness or heat, was visible and palpable. The lump was obviously fixed to the rib itself while the adjacent muscles and skin were quite free of the lump.

A thorough examination of the cardiovascular, respiratory and other systems proved negative.

Such is, more or less, the clinical picture of the condition when it presents itself to the physician.

SELECTION OF MATERIAL FOR STUDY.

For the purposes of the present paper, we have restricted our enquiry to fifty consecutive cases of this condition, encountered mostly in private practice and where facilities were available for frequent follow-ups of the patient.

After a critical analysis of our fifty cases, we are in a position to present our data.

RESULTS OF STUDY.

Aetiological Factors.

Sex and Age. (See Table I.)

The condition is apparently much commoner in women than in men. In the present series of 50 cases, there were 35 women to only 15 men, giving a ratio of 70% females to 30% males, or 2-3 females to 1 male.

TABLE I.—*The Age and Sex Distribution of our cases* (50 *cases*).

Age Group.	Age Distribution.		Sex Distribution.			
	No. of Cases.	Per Cent.	No. of males.	No. Of females.	% males.	% females.
0 – 9 Yrs.	0	0	0	0	–	–
10 –19 "	2	4	1	1	50	50
20 –29 "	10	20	4	6	40	60
30 –39 "	15	30	3	12	20	80
40 –49 "	12	24	3	9	25	75
50 –59 "	6	12	3	3	50	50
60 –69 "	3	6	1	2	33.3	66.6
70 –79 "	2	4	0	2	0	100
Over 80 "	0	0	0	0	–	–
For all Ages.	50	100	15	35	30	70

Apart from the very young and the very old, no age appears to be exempt from the condition. In our series, the disease showed a predilection for the fourth, fifth and third decades of life (in that order), these three-decades being jointly responsible for 74% of all cases. Only 22% of our cases were over the age of 50 years.

TABLE II.

Percentage Incidence of Various Aetiological Factors in Regional Costal Periostitis.
(Based on a series of 50 cases).

Feature Studied.		No. of Cases.	Percentage Incidence.
Aetiological Factors.			
Sex	Males.	15	30
	Females.	35	70
Age-Groups	1 to 29 years.	12	24
	30 to 59 years.	33	66
	60 years and over.	5	10
Racial Distribution.	Hindoos.	16	32
	Muslims.	4	8
	Parsees.	24	48
	Christians & others.	6	12
Body-build.	Hypersthenic.	5	10
	Hyposthenic.	17	34
Infections.	Acute rheumatic fever.	2	4
	Chronic rheumatic pains.	42	84
	History of colds, coughs, sore throat.	At least 40	Over 80
	History of syphilis.	4	8
	+ve W. R. (Only done 18 cases.	1	?
Other features:			
	Organic cardiovascular disease.	4	8
	History of exposure to "chill"	>36	>72
	History of local trauma.	8	16
	Sedentary habits.	7	14
Associated neurotic manifestations.		46 (?)	92 (?)
	Pyrexia	Occasional	and Slight.

There was apparently a higher incidence of males, in our series, both in the earlier age-decades (under the age of 30 years) and also in the 50 to 59 years age-group. The relative incidence of females, on the other hand, was much higher (ratio of 4 to 1) in the fourth decade of life.

Race.

Of our 50 cases, 48% were Parsees (24 cases), 32% Hindoos (16 cases), 8% Muslims (4 cases) and 12% (the remaining 6 cases) were composed of Christians and others. This apparently high incidence of the condition in a minority community is at least, in part, due to the fact that the great majority of my patients, in practice, happen to be Parsees.

Body-Build.

Whilst only 5 of our cases could be described as being of the "stout and stocky" type (hypersthenic), there were at least 17 who deserved the qualification of "thin and wiry" (hyposthenic), being associated with long chests and prominent ribs.

Habits.

The condition is apparently commoner in persons engaged in the normal pursuits of life than in those of indolent dispositions with sedentary habits. It is particularly observed in women who keep the upper part of the chest exposed by wearing "low-necked" or loose-fitting garments and indulge in exposure to inclemencies of weather. "A long drive in an open car" or "a bus-ride" or "getting drenched on a rainy day" may be the precipitating factor initiating the mechanism of pain in such patients. Next in importance to "exposure" or "chill" in the initiation of the trouble is perhaps "local trauma" or more often, long-continued summation of "minor traumata" (such as repeated manipulation or palpation of the affected region).

Respiratory and other Infections.

A history of acute rheumatic fever was elicited in only 4% of cases although chronic rheumatic ailments and vague aches and pains in diverse regions of the body were noted in at least 40 of our 50 cases. Actual deformities of rheumatoid type and of degenerative osteoarthritis are unusual, being witnessed in 16% (8 cases) of our series.

A history of "repeated colds" or coughs or attacks of bronchitis is common enough (over 40%). One gathers the impression that these patients show an unnatural predisposition to upper respiratory tract infections.

In 4 of our cases (8%) a history of syphilitic infection was observed, whilst of the 18 cases in whom a Blood W. R. or Kahn was obtained, the result was positive in only 2. Although, of the nature of a periostitis, the condition appears unrelated to syphilis.

Relation to Climacteric.

The probability of such a relationship is suggested by the relatively higher incidence of the disease in females, especially in the middle decades of life. Closer scrutiny of our cases serves to confirm this impression. There is no doubt that in the majority of female cases, the condition appears either at the time of the climacteric (which is often early or premature in these cases) or appears a short while prior to the cctual cessation of menses. In 4 of our cases, the condition was noted after an artificially induced menopause whilst in more cases than not, there is a history of some form of menstrual derangement extending over years.

Neurosis.

Nervous or neurotic manifestations, *e.g.*, palpitation, "painful breathing", tremors, cold extremities, frequent "flushes", "hot and cold feelings", insomnia, extreme vaso-motor and nervous irritability, all figure prominently in these cases. Brisk tendon reflexes and "hypersensitivity" to Libman's pain test are common findings.

Speaking of nervous manifestations and their multiplicity, we would like to recall the impression of Gallavardin[2], *viz.*, "The general impression left the physician is the extreme diffuseness of the manifestations ; there are so many things that there are too many."

Associated Cardiovascular Manifestations.

These, when encountered, are purely accidental and bear no direct relationship to the disease. In only 4 of our cases (8%), could we find evidences of organic heart disease ; hypertensive heart disease in 2 cases, rheumatic valvulitis in one and Angina of Heberden in one. The condition, although pertaining to the chest, has obviously nothing to do with lesions of the heart or lungs.

Subjective Manifestations. (See Table III)

The two symptoms, *par excellence*, of this condition are "local chest-pain" and local tenderness to palpation. Amongst the other symptoms complained of, often unrelated to the condition itself, nervous or vasomotor phenomena and "rheumatic pains" hold our attention.

The symptom of *local pain* is complained of, at some time or other, by every single case of the disease. The most striking characteristics of this local chest pain will now be enumerated, with a view to facilitate recognition of this clinical entity.

(1) The pain is strictly *local* and within the confines of the part or parts of the rib or ribs affected. In many cases, the actual seat of pain is no larger in dimension than a finger-tip.

(2) Though *continuous* in the majority of cases, the pain is liable to exacerbations and remissions. Whilst exacerbations are usually provoked by extraneous factors, remissions are as a rule spontaneous.

(3) Exacerbations of pain are particularly frequent after *exposure* to chill and draughts, after local injury or manipulation, after upper respiratory tract infections, during periods of fatigue or exhaustion and in relation to menses.

(4). The *character* of the pain varies from case to case and even in the same case from time to time, although the "stock expression" used by the patient, for the pain, in the great majority of cases, is a "dull aching pain", often described as "bruise-like" pain.

TABLE III. *Frequency or Percentage Incidence of Various Clinical Features in cases of Regional Costal Periostitis. (50 Cases).*

Feature Studied.	No. of Cases.	%
Symptoms:		
Local pain.	50	100
Continuous type.	app. 40	80
"Dull-Ache" type.	35	70.
Tenderness on palpation.	46	92.
Local hyperaesthesia.	app. 30	60.
Signs:		
Visible swelling.	18	36.
Palpable swelling.	50	100.
Left-sided.	38	76.
Right-sided.	9	18.
Bilateral.	3	6.
Involvement of 2nd and 3rd ribs.	33	66.
"Redness" or heat.	0	0

Occasionally, the pain is described as being "tooth-ache like", "gnawing", "burning", "boring" or even as "lancinating".

(5) The *intensity* of the pain is extremely variable, even in the same case. It may be so mild, it is hardly noticeable; on the other hand, it may occasion distress or even sleepless nights.

(6) The pain, even when continuous, tends to be maximal in the early mornings ("after a night's rest") and may show a second exaccerbation towards evening, especially "at the end of a heavy day".

(7) The pain is nearly always associated with local tenderness on palpation. In our series of cases, tenderness was obtained "by digital palpation with the finger-tips" in well over 90% of cases.

(8) Local hyperaesthesia accompanies the pain and tenderness in about 60% of cases. It can be elicited quite simply by "lightly dragging the head of a pin over the skin", as originally suggested by both Mackenzie[4] and Head.[3] The zone of hyperaesthesia is usually noted at the site of maximum pain and to a certain extent, around the region. In some cases, the hyperaesthesia may render the patient intolerant of even the touch of a finger or the gentle pressure of his bed-clothes or wearing apparel; this is particularly so during severe exacerbations. Paradoxically enough, other patients appear to derive comfort from the pressure of a "soft pillow" applied to the site of pain.

(9) Although warm *applications* may afford partial or even lasting relief in some cases, the great majority of patients are intolerant of and often react badly to "very hot packs" or to "intense local heat". An exception may be made in the case of "internal heat" as with short-wave diathermy, which not only affords relief from pain but may even cause early resolution of the painful swelling of the rib.

(10) The pain bears no relation to ingestion of meals and is not initiated by physical exertion, although it does tend to be "worse" after a "strenuous day". Isolation and emotional upsets are prejudicial to recovery whilst congenial surroundings and "pleasing occupation" may go a long way towards affording therapeutic relief.

(11) Refractoriness to treatment is often a characteristic of this form of pain. A case, apparently on the verge of recovery, may suddenly "relapse" after a minor indiscretion or chill.

Objective manifestations. (See Table III).

Physical examination of the patient, apart from revealing the local swelling or swellings of the rib, is negative, there being no other constant objective manifestations of the disease.

Both palpation and inspection are of value in determining the physical characteristics of the "swollen rib". The following characteristics (of diagnostic importance) require special mention:

(1) The ribs most frequently affected by the disease are the second, third, fourth, eighth and seventh (in that order of frequency). The second and third ribs alone accounted for 66% of our cases. (2) The rib-swel-

ings are encountered far more often on the left side of the chest, the localization being "left-sided" in 76% of my cases. In 18% the localization was "right-sided" and in 6% distributed "bilaterally". This high incidence of costal periostitis on the left side of the chest may be more apparent than real. Because of the inherent "fear of heart disease", patients with pain are much more likely to report to the doctor for pains on the left side of the chest than for pains situate on the right side. Pains on the right-side of the chest, are usually treated at home, with local remedies or with one or other of "grandmother's recipes". (3) The condition is encountered nearly always on the anterior wall of the chest, sometimes laterally and hardly ever posteriorly. This is probably due to the "factor of exposure or chill", which is far more likely in the former localizations. (4) The exact location of the rib-swelling is rather peculiar. When affecting the upper ribs (*i.e.* 2nd, 3rd or 4th), the fusiform, smooth and tender swelling is located usually just lateral to the costo-chondral articulation. When the affection is multiple, it often displays, on inspection of the chest, a "beaded" appearance. When the condition affects the lower ribs (*i.e.* 7th and 8th usually), the lumps are located much farther out along the rib, somewhere between the parasternal and the anterior axillary lines. (5) On careful scrutiny we find that the lump is firmly fixed to and "actually arises from" a rib; it is smooth, firm, about an inch or two in diameter and fusiform or rounded of shape. There is no local heat or redness over the lump whilst the adjacent intercostal muscles and skin are devoid of any affection or attachment whatsoever.

Apart from rheumatic deformities, elsewhere, in some of the patients, there are usually no other objective manifestations.

The frequency or incidence of the various symptoms and signs in our series of cases, have been presented in tabular form, in the accompanying Table III.

Diagnosis.

A correct diagnosis is dependent on the familiarity of the clinician with the existence and nature of the entity.

The differential diagnosis is (1) from the various other causes of localized chest pains, especially from the other varieties of so-called "left supra-mammary", or "upper left parasternal pains" (Vakil,[6] 1948) and (2) from the other causes of "Local swellings" in the region of the chest-wall, especially from swellings of ribs and costal cartilages.

Course.

This is very variable. With temporary remissions and relapses, the condition may drag on for months or years, often proving quite refractory to treatment. A proper regulation of the mode of life and habits of the individual with avoidance of "exposure", chills and minor traumata may go a long way towards shortening the course of this disease.

Treatment.

The treatment of this entity usually proves "long drawn out" and rather disappointing. After a fair trial of numerous therapeutic measures, in our series of cases, we cannot describe any one measure that can be labelled "specific" or "rapidly curative". A combination of the following measures is probably the best course to adopt, as the results yielded are quite "satisfactory":

(1) An important item in the programme is to protect the affected part from chills and "exposure" by the use of a flannel bandage or covering. Such protection should be continued for two or three months after apparent "cure". (2) The patient should train himself not to continuously palpate or manipulate the affected part; such a practice is almost universal and delays recovery; (3) Internal administration of moderate doses of sodium salicylate or aspirin or salol coupled with gradually increasing doses of potassium iodide, contributes greatly to recovery. My habit is to add tinct. gelsemii, 7 to 10 minims, per dose of the iodide-salicylate mixture. (4) The local pressure of a "soft pillow" may afford relief in some cases whilst in others, the application of "warm packs" are preferred. Internal heat (short wave treatment) is very effective and always worth a trial. Very hot applications and long-continued exposures to "radiant-heat" or infra-red lamps are likely to cause exacerbations of pain. (5) It is my practice to advocate, on alternate days, intravenous injections of iodide and salicylate (A. F. D.) and Calcibronat 10 c. c. (Sandoz); this may be continued, as a daily procedure, for even a fortnight at a time. (6) In the female cases and particularly in those at the time of the menopause or with "scanty menstruations", ovarian extracts (1 mg. Ovocyclin twice weekly, intramuscularly) may cause a remarkable amelioration in the clinical condition of the patient. The injections of Ovocylin may be continued, intermittently, over long periods of time. (7) In case of continuous, severe pain, I have sometimes resorted, with favourable results, to the injections of cobra venom, in graduated doses or to injections of "milk-protein" with the artificial production of pyrexial reactions.

SUMMARY AND CONCLUSIONS.

1. Attention is drawn to a fairly common but much neglected clinical entity, for which the suitable designation of "Regional Costal Periostitis" is proposed.

2. A clinical series of 50 consecutive cases of this type, personally observed, has been analyzed from the point of view of aetiological factors, symptoms and signs. Clinical criteria have been enumerated, whenever possible, in order to facilitate diagnosis.

3. In view of its apparent frequency and diagnostic importance a plea is made for a closer consideration, in future, of this entity.

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TREATMENT OF LOBAR PNEUMONIA WITH PENICILLIN OIL SALINE SUSPENSION

T. H. Tulpule *

Pneumococci are highly susceptible to the action of penicillin. Its value in the treatment of pneumonia (pneumococcal) has been established The disadvantage of the penicillin treatment is its frequent administration because of rapid excretion of the penicillin given in aqueous solution. The results are superior to those obtained with sulpha drugs.

Various methods were attempted to delay the excretion of penicillin with the hope that the number of injections could be reduced without reducing the efficacy of the treatment. The commonest method is that of suspension of penicillin in beeswax peanut oil mixture (Romanawsky's formula) with a single injection of 300,000 units of penicillin suspended in beeswax-oil mixture. The excretion is prolonged to 24 hours and treatment of conditions like uncomplicated gonococal urethritis can be successfully treated.

Cannon and his colleagues reported that 1.5 million units of calcium penicillin suspended in hydrogenated cotton seed oil would maintain a penicillin blood level of 0.1 unit per c. c. of blood for twenty-four hours or longer. Encouraged by this report it was decided to try locally prepared similar oil preparations. Unichem Laboratories, Bombay, prepared a diluent from sesame oil. This diluent was viscid enough to slow the absorption yet such that it mixed well with water to form an emulsion.

An emulsion of penicillin-saline-oil was prepared in the following way. The required amount was dissolved in one mililitre of saline which was mixed with equal quantity of the diluent of the sesame oil. The mixture was thoroughly shaken for five to seven minutes to form emulsion of fine particles and was quickly injected intramuscularly.

Tests were improvised to find out the period of excretion of penicillin in urine when given in above described suspension form. The method adopted was as follows: A twenty-four hour old culture in broth of staphylococcus (Oxford strain) was obtained and was poured on an agar plate. Small glass cups were put on the plate. If the plate was big, it would hold two or three. A penicillin solution containing 4 units per c. c. was prepared. In one cup this diluted penicillin was put and in the other the urine to be tested. The agar plate was incubated for 24 hours and at the end of that period the results were noted. A clear zone formed around the base of the glass cups; the diameter of the zone varied with the amount of penicillin in the cup, in standard solution or in the sample of the urine. The results of this test are given in table No. 1. From this it was concluded that sufficient amount of penicillin to inhibit the growth of staphylococcus was found in the urine of a person who was given, 250,000 or 200,000 units of penicillin, given in saline-oil emulsion at the end of 17 or 18 hours. This saline-oil emulsion of penicillin was used in the treatment of two cases of uncomplicated gonorrhoea. The dose was 250,000 units of penicillin in saline-oil suspension. The results of treatment were completely successful and encouraging.

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TABLE I

	Case.	Amount of penicillin given in oil-saline suspension.	Hours of collection of urine after the injection of penicillin-oil-saline suspension.	Millimeters of clear zone around the cups treated with	
				control penicillin solution 4 units per c. c.	Urine of patient given penicillin oil-saline suspension.
1.	Gonococcal urethritis	250,000	12 hours	7	15
2.	Gonococcal urethritis	250,000	12	6	14
3.	Stab wound of abdomen	200,000	12	8	14
4.	Paraplegia	200,000	12 16	4 –	16 12
5.	Paraplegia	200,000	13 17	4 –	15 12

Penicillin-saline-oil suspension prepared as mentioned above was next used in the treatment of 30 cases of acute lobar, uncomplicated pneumonia. The patients were admitted in Sir J. J. Hospital. The criteria for diagnosis of pneumonia were (1) signs of consolidation, i. e. diminished movement, increased tactile vocal fremitus, impaired or dull note, bronchial breathing and crepitations. (2) shadow of consolidation on screening of chest under X-rays (3) the presence of leucocytosis in the blood. When the above criteria were satisfied as regards the diagnosis of lobar pneumonia, the penicillin therapy was instituted. No special selection of cases was made. A single injection of 250,000 units of penicillin suspended in saline and oil was given. Twenty-four hours later another similar injection was given. No other treatment was given. Temperature came to normal within 24 to 36 hours of the first injection of penicillin-saline-oil suspension. This was accompanied by all round improvement in general condition of the patient. Most of the symptoms decreased in their severity but the physical signs in the chest persisted. Twenty seven cases out of 30, showed such improvements. Table II shows the response of cases of pneumonia to the penicillin-saline-oil suspension.

TABLE II

Total number of pneumonia cases	Good response	Delayed response	Relapse or recrudescence of symptoms
30	26	1	3

Good response :—Temperature settled to normal within 24 to 36 hours of the therapy with concommitant improvement in general condition.

Delayed response :—When the temperature settled to normal in longer than 48 hours.

Relapse :—If there was recurrence of the symptoms and signs and pyrexia after the temperature was normal for a few days.

The following cases are described in detail as they show interesting features :—

CASE No. 1. A male aged 40 was admitted with a history of fever, cough, breathlessness and pain in the right side of the chest of four days duration. He was dyspnoeic. Temperature was 104°F, respirations were 32 per minute and pulse 120 per min. The tongue was dry and coated, skin was hot and dry. Examination of respiratory system showed signs of pneumonia in the right middle zone. Flouroscopy of chest confirmed the presence of consolidation in the right side. Total number of leucocytes was 10,000 per c. mm. Injection of 250,000 units of penicillin-saline-oil suspension was given. Twenty-four hours later the temperature was 99°F, pulse 100 per min. and respirations 26 per min. General condition was very much improved. Another similar injection of penicillin-saline-oil suspension was administered. Temperature settled to normal 48 hours from the beginning of the therapy and patient's condition had improved so much that he was sent home at his request 3 days after his temperature was normal.

CASE No. 2. A male aged 28 was admitted to the hospital on the fifteenth day of the illness. He was drowsy and was not able to give proper history. His temperature was 97°F, pulse 88 per min. and respiration 22 per min. Signs of lobar pneumonia were found at right base on examination of the respiratory system. There was rigidity and tenderness in the right hypochondriac region of the abdomen. There was nothing abnormal detected on examination of the other systems. Four hours after the admission temperature was 103°F, pulse 130 per min and respirations 35 per min. He was given 250,000 units of penicillin-saline-oil suspension once a day-for two days. The temperature in this case touched normal 90 hours after the first injection of penicillin. The response to the treatment in this case was considered as a delayed one.

CASE No. 3. A forty years old male was admitted for fever, breathlessness and cough, with pain on the left side of the chest of two days duration. His general condition on admission was very low, temperature was 99°F, pulse 130 per min. and respirations 40 per min. His blood pressure was 60 mm Hg/40 mm. There was signs of lobar pneumonia on the left side. Total number of leucocytes were 13,800 per c. mm. He was given 250,000 units of penicillin-saline-oil suspension once, on two consecutive days. The temperature dropped to normal within 48 hours and remained so for 2 days. Later he had recrudescencc of symptoms and signs of pneumonia with an increase in pulse rate and respiratory rate. This time he was successfully treated with usual dosage of sulphadiazine. He was observed for 10 days during which period he was normal but signs in the lungs persisted.

CASE No. 4. A case of lobar pneumonia of right lower lobe was admitted on the fifth day of the disease. He was given 250,000 units of penicillin-saline-oil suspension on two consecutive days. At the end of thirty-six his temperature was normal. Forty-eight hours later he had a rise of temperature for a few hours which settled to normal with sulphadiazine.

CASE No. 5. Male aged 40 was admitted for lobar pneumonia of the right lower lobe on the 4th day of the fever. Total leucocytes were 13,400 per c. mm. He was given 250,000 units of penicillin-saline-oil suspenson in one injection, on two consecutive days. His temperature settled to normal within 36 hours and remained normal for 48 hours. Later he ran a low temperature for 8 days unaffected by further treatment with two injections of penicillin-saline-oil suspension. Signs of unresolved pneumonia persisted, the patient could not be observed as he left the hospital against medical advice.

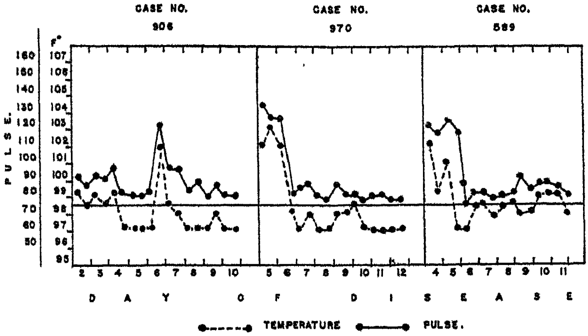
Recrudescence of temperature as seen in cases 3 and 4 has also been observed by other authors in the treatment of pneumonia with penicillin. In case No. 5 the possibility that the infecting organism had become resistant to penicillin could not be excluded.

LOCAL REACTION: (1) there was slight pain perceived by most of the patients at the site of the injections. (2) No injection abcess was observed in our series.

CONCLUSIONS.

(1) 30 cases of lobar pneumonia were treated with 250,000 units of penicillin-saline-oil suspension, given in one dose on two consecutive days.

(2) The treatment was successful in 26 cases. There was a delayed response in one and recrudescence of symptoms and signs in 3 other cases.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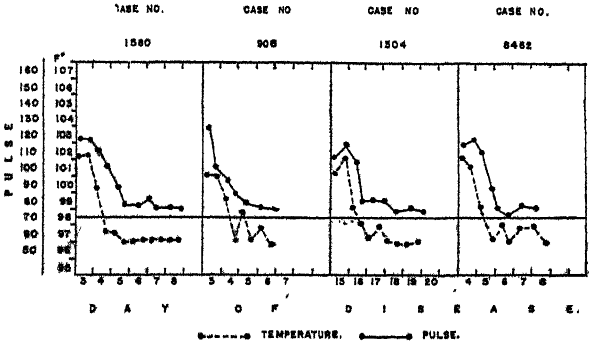
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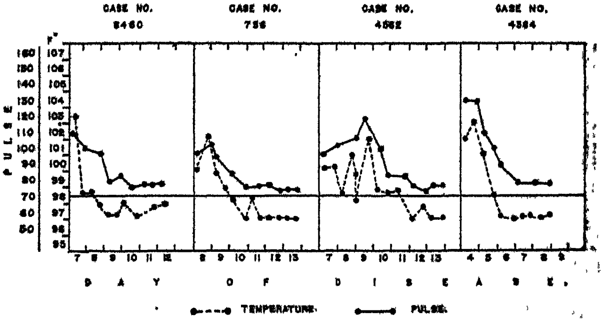
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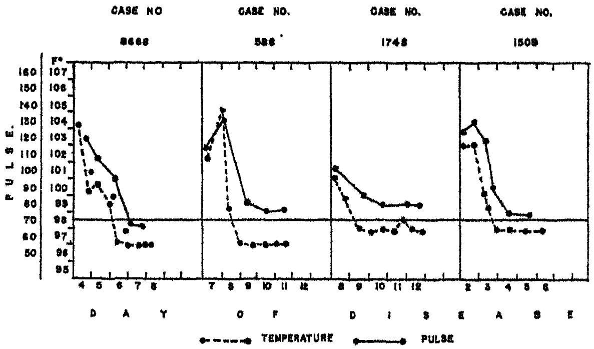
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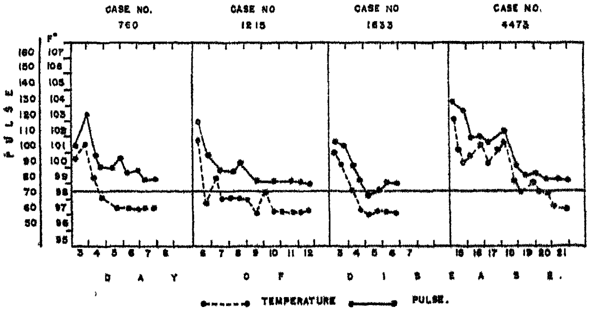
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NUTRITIONAL MEGALOBLASTIC (MACROCYTIC) ANAEMIA

Y. M. Bhende*

Historical and Nomenclature.—In the first serious study of the so-called "pernicious anæmia of pregnancy" in India, in 1930, Wills and Mehta[215] came across an anæmia which was macrocytic in type but distinguishable from addisonian pernicious anæmia by different age and sex incidence, the absence of the characteristic glossitis and cord lesions and lack of any rise in the serum bilirubin level as judged by the Van-den-Bergh reaction, and, by the presence of free hydrochloric acid in the gastric juice. The same condition was encountered in five non-pregnant females and this led the authors to predict its possible occurrence in the general female population of India. They further quoted Sokhey[165] as having found a similar condition in the male population of Bombay. An enquiry into the dietetic history of their patients suggested that the anæmia might have been due to some dietary deficiency, pregnancy merely acting as a precipitating factor. Subsequent studies, a few months later, (Wills and Talapade[220], Wills and Mehta[216, 217]) supported these views. In 1931, Wills[203] discovered that marmite was curative for this type of anæmia, thus establishing its nature as a deficiency disease. Believing it to be a disease *sui generis* she named it "tropical macrocytic anæmia" (T.M.A.). In retrospect, it may be said, that this anæmia had been noted by several observers before Wills and Mehta[215], though, of course, its identity had not been established. Thus Mackie[112] as early as 1906, had noticed "a severe and often fatal anæmia not confined to pregnant women nor to sprue patients, but found also in non-pregnant females and males, of the nature of aplastic anæmia and often megaloblastic in type"; he distinguished it from addisonian pernicious anæmia on both clinical and hæmotological grounds, and, called it "malignant anæmia of the tropics". Likewise, some cases of "anæmia of pregnancy" described by Mudaliar[125] in 1914-15 and by Balfour,[7] McSwiney[118], and, Ghosal,[71] in 1927, and, by Fairley[61, 62] in 1931 may have been cases of T.M.A. This is even more probable of the series of cases observed by Vaidya[194] in Bombay in 1930 and classed by him as "pernicious-type anæmia". Prompted by Wills'[203], demonstration of the efficacy of marmite in T.M.A., Strauss and Castle[174] (1932) considered the possibility of marmite containing their extrinsic factor; their investigations supported this thesis and T.M.A. came to be looked upon as a macrocytic anæmia due to the deficiency of the extrinsic factor in the diet. Napier's[131] (1936) experience was not in accord with this concept and he postulated deficiency of an independent hæmopoietic factor as the underlying basis for T.M.A. encountered in India, a suggestion which Wills and Evans[214] accepted by 1938. At the same time, Napier[131] broadened the original concept of Wills and Mehta[215] by describing two distinct subgroups: the non-hæmolytic, which answered to the original description of Wills and Mehta[215]; in the other, the hæmolytic group, malarial infection played a significant rôle in the aetiology. For both these groups, however, he retained the original designation T.M.A. In 1937, Gröen and Snapper[78] described 2 cases of macrocytic anæmia of dietary origin and suggested that this type of anæmia be preferably called "macrocytic dietary deficiency anæmia". Fairley, Bromfield, Foy and Kondi[64] (1938) investigating pregnancy anæmia (macrocytic) in Macedonia confirmed Napier's[131] contention of the non-hæmolytic and the hæmolytic subgroups and described a third 'aplastic' type; they further suggested that T.M.A. be renamed "nutritional macrocytic anæmia" (N.M.A.) During the discussion that followed this paper presented before the Royal Society of Tropical Medicine and Hygiene, Wills[208] contended that her term T.M.A. should either go by the board or be retained for the tropical cases as a subsection of the generic term N.M.A.; but, Napier[138], in the same discussion, remarked that in view of the incomplete knowledge of the ætiology of T.M.A. time was not ripe for a revision of the then current nomenclature. Alstead[2] (1939) studying a single case of macrocytic anæmia of dietary origin called it "exogenous pernicious anæmia" under the belief that in his case the anæmia resulted from an ultimate lack of the anti-anæmic principle consequent on deficiency of the extrinsic factor in the diet. Trowell's[184,185,187] (1942-1943) experience in South Africa drove him to the conclusion that the deficiencies in the tropics were usually multiple and that this held good for N.M.A. as well. The most common type of anæmia in his material was what he chose to call "dimorphic anæmia"—"an iron deficiency anæmia complicated by N.M.A., or, may be equally well regarded as N.M.A. complicated by iron deficiency". The name N.M.A. applied as a generic title seemed hitherto as the most accepted one till Watson and Castle[199] (1946) extended its use "to include addisonian pernicious anæmia and macrocytic anæmias of pregnancy, sprue, fish-tapeworm infection, and so forth, as well as, the anæmias more obviously associated with dietary deficiencies presumably including Wills' factor and the so-called extrinsic factor". This would mean that the term N.M.A. includes all the macrocytic anæmias due to both direct and conditioned deficiencies of the anti-anæmic principle, and, as such, is apt to lead to confusion.

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The expressions T.M.A. and N.M.A. have crept into the literature without any exact definition either of the clinical syndrome(s) connoted by these terms or a precise description of the hæmatological picture (s) they signify[131]. It is probable, almost certain, that macrocytic anæmias due to deficient diet constitute a complex group. Theoretically, it should be possible to split the group on the basis of the specific factor lacking in individual cases. For practical purposes this must wait till the exact chemical constitution and the precise mode of formation in the body of the anti-anæmic (liver) principle are known, and, the various fractions that build it up are isolated in pure form.

On grounds of priority, T.M.A. has strong claims a. a suitable designation for the group of macrocytic anæmias due to deficient diet. However, Wills'[203] T.M.A. as originally described by her, was essentially a non-hæmolytic anæmia, and as pointed out by Fairley, *et al.*[64] the inclusion of the hæmolytic sub-group under the same title would hardly be correct. Besides, as the same condition is encountered outside the tropics,—in fact, it is met with in all climates—the term, again, is not appropriate. Enough evidence is available to show that the anæmia under consideration may not be always macrocytic and the only infallible criteria for its diagnosis are either the presence of a true megaloblast in the peripheral blood or the presence of megaloblasts in the marrow. The name nutritional *macrocytic* anæmia, is, therefore, strictly speaking misleading. Bearing in mind its ætiology and its unequivocal hæmatological characteristics, a suitable name would be *Nutritional Megaloblastic Anæmia* (*N. M.A.*). The anæmia will be so-called in this review. Obviously addisonian pernicious anæmia should be excluded from this group. Further, the name should be restricted to uncomplicated megaloblastic anæmia of nutritional (dietary) origin; megaloblastic anæmias seen in coeliac disease, tropical and non-tropical sprue, pellagra, intestinal disorders etc., should be separated from this group[210]. The so-called pernicious anæmia of pregnancy, as seen in this country, is, undoubtedly, nutritional in origin and this is true for the majority of the cases seen in the western countries. It is included under the term N.M.A.

In this review an attempt is made to assess the present status of N.M.A. Certain difficulties are inherent in such a project. Among the major ones may be mentioned: 1) in the older reports the hæmatological details are incomplete, 2) under the so-called pernicious anæmia of pregnancy apparently, all kinds of severe anæmias have been included, 3) the same cases of N.M.A. may have been included in different reports illustrating the various aspects of the disease process. The quantitative part of the analysis made is, therefore, not accurate. Though the problem of N.M.A. will be reviewed as a whole, the work done in this country will be emphasised.

Geographic Distribution: As dietary deficiency plays the prime rôle in the ætiology of this anæmia, it is scarcely surprising to find that the distribution is global. Further, poverty, ignorance, personal idiosyncrasies, and religious and social tenets will be significant factors in determining its frequency in various parts of the world. In India cases have been reported from all corners. Wills and her co-workers [203, 206, 215, 216, 220] drew their material from the Bombay Province. Balfour,[7] Mackie,[112] Sokhey,[165] Vaidya,[194] Dhayagude and Khadilkar,[54] Bhende,[12] Bhende and Patel,[14] Patel,[154] Kothari and Bhende[105] etc., studied their cases in Bombay. Mudaliar,[128] Mudaliar and Menon,[129] Mudaliar and Narsinha Rao,[130] McRoberts Reddy and Subramanium,[117a] Sunderam[180] etc., have reported cases from the Madras Province. The patients studied by McSwiney,[118] Mitra,[122, 123] Gupta,[78a] Napier and his colleagues[131, 136, 137, 144, 146], Chatterjee and Basu[26], Das Gupta[37], Das Gupta *et al.*[39], Goodall, Goodall and Banerjee[75], etc., were from the Bengal Province. Napier and Billimoria,[139] Napier and Mujumdar[145], Napier[132], Hare[80-82], etc., encountered N.M.A. in the labour population of the Assam Province. Upadhyay[193] described cases from Bihar. Chaudhary and Manglik[28] have reported it from the United Provinces, Nayer[148] from Delhi, and, Taylor and Manchandra[182] from the Punjab. Modi[124] encountered it in the Baroda State. No part of India is spared as is clearly disclosed by its prevalence in the Indian soldiers[33, 115, 164, 181, 198], and this may be correlated with the extreme poverty of our country as a whole. Its incidence will certainly vary in different parts of the country, determined as it is mainly by the dietary habits. In our neighbourhood, cases occur in the Indian Malay States[64, 203], China[203], and Mauritius[163]. From Africa, a region of the world where malnutrition abounds in the non-European population, N.M.A. has been described by several observers[72, 159, 183, 184, 185, 187]. In Europe, the largest number of cases have been reported from Greece (Macedonia)[64]. Gröen and Snapper[78] encountered their 2 cases of "macrocytic dietary deficiency anæmia" in Holland. Only a few cases of N.M.A. (the so-called pernicious anæmia of pregnancy excluded) are recorded in the United Kingdom.[189,191]. Wills[208] believed it was common in the North of England. It is not unlikely that many cases are missed, and, others reported as "pernicious anæmia with return of hydrochloric acid and ferments after treatment[41]" or "pernicious anæmia without achlorhydria[127]" may have been, in fact, cases of N.M.A. In this connexion, McRoberts[117] has asked a pertinent question: "I wonder how many people in England today are receiving conscientious and regular liver treatment for non-addisonian anæmia ?" Trowell [185] warned that the war exigencies would increase its prevalence in Great Britain and Europe, but a recent annotation in the LANCET[109] has assured that N.M.A. continues to be uncommon in England and that it is confined to the homes for the mentally defectives. In the continent of America, Spies[168] thinks, that N.M.A. is seen uncommonly in the north temperate zone, but is quite frequently encountered in the south temperate zone and in the tropics. It is quite prevalent in the British Guiana[72] (among the East-Indians), in Birmingham, Alabama[126a],[168],[171], and in Puerto Rico[157]. It is not uncommon in the West Indies[188].

Incidence Among the Various Communities In India: Wills and Mehta[215] found that N.M.A. was prevalent in all the communities—Hindus, Mohomedans, Christians and Bene-Israels but was seldom met with in the European residents. Balfour's[7] series of 150 cases contained 59 Hindus, 52 Moslems, 29 Indian Christians, 7 Jews, and 3 Parsees. When these figures were expressed in terms of the number of admissions (to the maternity hospitals) from the different communities, it was calculated that 10.2 per cent. of the Moslem mothers were affected compared to the 4.1 per cent. of the Hindu and 4.4 per cent. of the Christian mothers. Gupta's[78a] larger series of 203 patients, in a similar comparison, showed that Moslems were affected more than the Hindus and the highest incidence was among the Indian Christian community. Without any such comparison, Mudaliar and Narsinha Rao[130], McSwiney[118], Mitra[122], and, Napier and Neal Edwards[146] found N.M.A. commoner among the Hindus than the Moslems, while Wills and Mehta[215] thought that the distribution to be exactly the opposite. Chaudhary and Manglik[28], working at Agra, opined that the incidence among the two major communities was equal. Cases among the Eurpoean residents in India, though few, have been recorded[117, 131]. It is apparently commoner among the Anglo-Indian community[78a, 118 131]. There is no large series reported to work out the incidence among the males of the different communities. In any case the economic state, the dietary habits, and, religious or social prejudices of the population have more to do with the incidence of N.M.A. than any constitutional factors peculiar to the various communities[146,210]. The large number of cases reported in the Indian sodiers and the Indian prisoners of war [115,164,198] supports this argument. Though it is commonest among the poorer classes in India, it is not confined to them[7,146,215] and the yield from the middle classes is by no means insignificant[28,146]. Lastly, N.M.A. is the commonest megaloblastic anæmia met with in this country[14], in contrast to addisonian pernicious anæmia which is rare.

Age Incidence : Balfour[7] found that 13.6 per cent. of her patients were below the age of 20 years, 61.2 per cent were between 20 and 30 years, 22.6 per cent. between 30 and 40 and only 2.6 per cent. over 40. Combining the series of Balfour[7], McSwiney[118] and Mitra[122] the age incidence for 279 patients works as follows : 10.4 per cent. between the ages of 15 and 19 ; 64.5 per cent. between 20 and 29;20.1 per cent. between 30 and 39 ; and, 5 per cent. between 40 and 45 years[92]. Thus, full 75 per cent. of the cases fall in the age group of under 30 years. Wills and Mehta[215] had the same experience. The majority of the ptients studied by Mudaliar and Narsinha Rao[130] were between 20 and 30 years of age. Gupta[78a] and Chaudhary and Manglik[28] found the highest incidence between the age group 15 to 20 years. Analysing cases of anæmia in pregnancy, Napier and Neal Edwards[146] came to the conclusion that the incidence of severe anæmia was significantly greater in the age group 20 to 30 years than the other age groups and that there was a greater tendency for macrocytic anæmia to occur in the younger age groups. In considering the age incidence among the pregnant females—as in all the series quoted so far—the close association of age with parity must not be lost sight of[146]. Though no concrete figures are available, the age incidence among the males and the non-pregnant females would appear to be similar. Mackie's[112] youngest patient was a male 14 years old. In Napier's[181] series the majority of the patients fell in the age group 20 to 30 years, and Napier *el al.*[144] found the youngest patient to be 16 and the oldest 41. Wills and Evans[214] gave the age limits between 20 and 40 years. The age limits of Trowell's[187] patients of dimorphic anæmia varied from 16 to 60 years, the average was 27. In a recent series studied by Spies *et al.*[171] the patients' ages ranged from 35 to 70 years . At the other end Das Gupta *et al*[39]. have recorded N.M.A. in a child 9 years old, while Giglioli[72], in a series of 51 patients, encountered 6 below the age of 12 years and 1 case in an infant aged 11 months. Anderson and Roberts[4] have desribed N.M.A. in an infant 8 months old. In the megaloblastic anæmia of infancy described by Zuelzer Newhall and Hutaff[226] the ages of the patients ranged from 5 weeks to 1 year ; all of these reacted to folic acid, Cole's[29] case in an infant 3 weeks old fed on a deficient diet since birth, is probably the youngest recorded in literature; megaloblasts were present in the peripheral blood and the gastric juice contained free hydrochloric acid. The hyperchromic anæmia responded to Anahæmin.

Sex Incidence: Though Wills and Mehta[215] were studying the so-called pernicious anæmia of pregnancy, in their very first series, they came across 5 non-pregnant females showing the same features, and they quoted Sokhey[165] as having seen a similar anæmia in the male population of Bombay. Mackie's[112] patients suffering from "malignant anæmia of the tropics" were all males. Later Wills[206] analysing a series of 113 consecutive cases of N.M.A. found that 44 or 39 per cent were males, and, in another series, 32 out of 61 or 52 per cent. were males. She concluded, that in spite of the predisposing factor of pregnancy, the incidence of N.M.A. was the same in the two sexes. However, Giglioli[72] in British Guiana, found that if pregnant females were included the rate of females to males was 5.5 : 1. Napier[138] attributed the apparent preponderance of the females to the associated pregnancy and opined that if such pregnant cases be excluded, the ratio changed in favour of the males. In Mauritius, Sippe[163] encountered N.M.A. almost equally in both the sexes. Trowell's[187] first series of dimorphic anæmia contained 53 males, 2 pregnant females, and 3 non-pregnant females; in his second series, 36 were males and 14 females. Moore *et al*[126a]. remarked that in the tropics N.M.A. was apparently commoner among females and appeared quite frequently in association with pregnancy, but, their experience in Birmingham, Ala. was, that in a series of 56 cases N.M.A. affected the males three times as frequently as the females. Das Gupta's[37] small series of 25 was comprised of 21 males and 4 females. Kemp's[102] patients were all males. Among 82 consecutive cases of N.M.A. Patel and Bhende[156] found that 57 were males and 25 females.

Seasonal Incidence: Many authors[7,122,123,137,138,215] believe that as far as the pregnant cases are concerned, there is a peculiar high incidence noticed at certain times of the year. Majority of the workers put this in the second half of the year. Wills[210] remarked that this variation may be related to humidity, temperature, changes in the diet, marriage customs and the incidence of parturition. No author has commented on any seasonal incidence as far as N.M.A. in the males is concerned.

It may be summarised that N.M.A. can be encountered in any part of the world. Malnutrition from any cause determines its incidence in any country, race or community. It may occur at any age, but the highest incidence is in the adults. Both the sexes are affected, but the pregnant female is specially predisposed. In contrast to addisonian pernicious anæmia[202,224], in N.M.A. constitutional factors are of no significance and no familial incidence has been reported. Environmental factors alone are of importance.

SYMPTOMS

Wills and Mehta[215] commented on the paucity of the symptoms and signs other than those to the anæmia *per se.* The onset is insidious, the evolution gradual. It is remarkable how patients with the red cell count in the neighbourhood of a million per c. mm. come walking to the hospital, quite unmindful of the serious deterioration of their health[64,215]. General weakness, œdema of the ankles, a sore tongue, gastro-intestinal disturbances, and attacks of fever are the common symptoms.

Generalised Weakness, lasting from a few weeks to a few months, is a symptom volunteered in severe cases, but in mild ones its presence can be elicited only after specific questioning. Accompanying this, in the more severe cases, is the *Loss of Weight*; this is in contrast to addisonian pernicious anæmia, but in common to pellagra, beriberi, riboflavin deficiency, and sprue[168,169]. Napier[131], however, found that for his age and height no patient in his material was below the normal weight. Fairley *et al*[64]. and Giglioli[72] had the same experience. Our experience is not in accord with this and further we find that within a few days of the commencement of the treatment, the patients regain their appetite and by the time of their discharge from the hospital they have gained a good few pounds in weight[156]. Spies *et al.*[168,171] have similarly noted this occurrence.

Oedema of the ankles, extending for a variable distance up the leg, is not at all uncommon in fairly advanced cases of N.M.A. There may be puffiness and swelling of the face in addition[7,215]. A few cases—severe ones—have shown effusion into the serous sacs[89]. If marked, œdema may be the presenting symptom; if slight, careful examination alone can detect its presence. Balfour[7] found œdema in every one of her patients and so did Chaudhary and Manglik[28] in their material. In Mitra's[122] first series it was present in 77.9 per cent. of the patients; in his second[123] it was even commoner. Others have similarly commented on its great frequency.[6a,18,64,78a,126a,130,131,168,181,185,192,194,214,215] Napier and Neal Edwards[146] observed that in anæmias of pregnancy œdema could be correlated positively with the degree of anæmia and the size of the red cell. The usual explanation for the œdema is the reduced osmotic pressure of the plasma consequent on hypoproteinæmia, and, in advanced cases, the added factor of cardiac failure. However, Bachet[6] found that in early cases of nutritional œdema there was neither hypoproteinæmia nor cardiac failure, and, he argued that nutritional œdema starts in the tissue cells—it is due to insufficiency of the protein in the diet leading to a deficiency of albumin in the tissues. Interference with the proper function of the vascular endothelium (due to deficiency of vitamins) is yet another factor to be remembered[108a]. Oedema and even effusions in serous sacs may first appear with the regeneration of the red cells following treatment because of hypoproteinæmia produced during rapid hæmoglobin synthesis in the face of an inadequate protein intake[50, 89]. Patel[154] noted that in his patients of N.M.A. the œdema improved on a milk diet, and, if at this stage the patient was given a full vegetarian or a mixed diet the œdema tended to return.

A sore tongue or a sore mouth, *Glossitis* or *Stomatitis* is another common symptom in N.M.A. The frequency of this symptom varies. Balfour[7], Wills and Mehta[215], Wills Cluttebuck and Evans[213], Wills and Evans[214], Napier[131, 136, 137, 138], Chaudhary and Manglik[28], Chatterjee[23], Russel[159], Callender[18] etc., have pointed out the infrequency of this symptom as compared to addisonian pernicious anæmia. On the other hand, Mitra[122], Mudaliar and Narsinha Rao[130], Giglioli[72], Miller and Studdert[121] Moore *et al*[126a], Bhende and Patel[14], etc., observed it quite frequently. Balfour[7] found it in 31 per cent of her patients; the tongue showed red papillæ at the margins or on the surface and occasionally the papillæ were swollen, or, the whole tongue was red and raw. Mackie[112] noted that the tongue was pale and flabby but not irritable as in sprue. Mudaliar and Narsinha Rao[130] stated that glossitis, in some form or other, was present in majority of the cases. Gupta[78a] described the tongue as glossy and flabby but added that soreness was not always present. Napier[136, 138] remarked that the raw beefy tongue of addisonian pernicious anæmia did occasionally occur in N.M.A., but on the whole, apart from some tenderness, sore tongue and glossitis were not so common nor characteristic of N.M.A. Later, Napier and Neal Edwards[146], however, admitted that in N.M.A., in pregnant females, the mouth may be sore and the tongue may have a shiny smooth appearance with red raw patches. Atrophic glossitis—a smooth glazed tongue—would appear, from the descriptions of most workers to be rarely encountered in N.M.A. Walters *et al*[198]. studying malnutrition in the Indian prisoners of war, described two lesions in the tongue in N.M.A. ; in one the tongue was swollen, indented by teeth, fiery red, sore, burning and tender—this type they attributed to riboflavin deficiency ; in the other, produced by nicotinic acid deficiency, the tongue showed atrophy of the epithelium and papillae, and, the organ was glazed and pointed, with burning as a prominent symptom but without any tenderness. Manson-Bahr[114] pointed out that deficiency of vitamin B complex was common in sprue and addisonian pernicious anæmia and accounted for the glossitis, cheilosis, sore tongue and paraesthesia. In his opinion, if these symptoms did not respond to the administration of the liver principle alone, addition of vitamin B complex as an adjunct to therapy was justifiable. There is even more reason to believe that deficiency of some factor in the vitamin B complex is concerned in the aetiology of N.M.A. and the infrequency of glossitis and stomatitis recorded by many observers becomes difficult to explain. Glossitis and stomatitis respond promptly to marmite or liver therapy. Folic acid is reported to relieve it as quickly as liver[168,171] but recent reports show that in addisonian pernicious anæmia at least the glossitis may recur while the patient is still on folic acid maintenance therapy[88,197]. Thymine or methyl uracil does not constantly relieve it[68,168]. Darby[35] has pointed out that though a deficiency of riboflavin, niacin and other members of the vitamin B complex may and sometimes does give rise to glossitis and cheilosis, iron deficiency may be yet another causal factor.

No convincing explanation has been offered for the digestive upsets in N.M.A. and the related anæmias resulting in *Vomiting* though the consequent deleterious effect on the patient's general condition and his anæmic state is freely admitted. That vomiting of pregnancy by depriving the sufferer of essential nutriments plays some part in the ætiology of anæmias in pregnancy is universally acknowledged [18,138,202,224]. But vomiting occurs in the so-called pernicious anæmia of pregnancy in later months, long after the physiological vomiting has ceased[7,129], and, vomiting is noted in the non-pregnant females and the males suffering from N.M.A. as well[7,126a,136,156,168,203]. Napier and Neal Edwards[146] analysing all types of anæmia in pregnancy, observed that vomiting was most commonly associated with the macrocytic type. The vomiting may be continuous or in attacks, with intervals of freedom. Accompanying the vomiting there may be a sense of nausea[137,168], loss of appetite, and dyspepsia in some form or other[14,131,136,138,156]. The last may take the form of heaviness or pain in the epigastrium or abdomen after food, flatulence, eructations, and distention. A particular distaste for meat has been described[163], but, its significance in our country is little as many of the patients are strict vegetarians and have never tasted eggs or flesh.

Among the gastro-intestinal disturbances, *Diarrhoea* is common but its frequency and severity varies from case to case. It may be present in attacks, or, on the other hand there may be passage of somewhat loose stools without any real frequency. No blood or mucus is passed in uncomplicated cases, nor is there any tenesmus. The faeces are usually watery or semi-solid; they are neither bulky nor frothy and chemical estimations do not show an excess of split or unsplit fat[64,198,210]. Bilious stools have been described in the haemolytic form of N.M.A.[64]. Balfour[7], Wills and Mehta[215], Mitra[122,123], Chaudhary and Manglik[28], Moore *et al.*[126a]. Spies[168], Bhende and Patel[14], Taylor and Manchandra[182] Spies *et al.*[171] etc. have remarked on the great frequency of diarrhoea in their material (20.6 to 74.1 per cent). Napier[131] however found that dyspepsia was common but diarrhoea was present in few cases. Same was the experience of Giglioli[72] in British Guiana and of Walters *et al.*[198] studying N.M.A. among the returned Indian prisoners of war. Later, Napier and Neal Edwards[146] discussing anaemia in pregnancy admitted that diarrhoea was more commonly associated with macrocytic anæmia than the other types. Reviewing her total experience, Wills[210] opined that in some years in Bombay diarrhoea was not a common complication though severe cases of anæmia were frequent; in other years it was very common. Her experience in monkeys in which she had reproduced N.M.A. by deficient diet was the same[210]. Balfour[7] and Mitra[122] have remarked that diarrhoeic cases show a higher mortality among the pregnant females than the non-diarrhoeic. Diarrhoea and vomiting were present in 40 to 50 per cent of Callender's[18] cases of the so-called pernicious anæmia of pregnancy in the West. Diarrhoea is a common symptom in addisonian pernicious anæmia[209,224] occurring in about 50 per cent of the cases and has been related causally to the achlorhydria constantly present in that condition. The diarrhoea in N.M.A. responds to marmite (marmite does not affect the diarrhoea of cœliac disease[195].) liver extracts, nicotinic acid and folic acid and the related compounds[19,28,100,168]. Folic acid, similarly, checks the frequency of bowel action in sprue without greatly modifying the biochemical defects in the faeces[49], and Carruthers[19] found it effective in 6 cases of diarrhoea of varied aetiology ; in the experience of the same observer crude liver extracts and large doses of yeast have been definitely effective in many cases of chronic diarrhoea unrelated to anaemia. Davidson[40] believed that marmite toned up the intestinal tract and increased absorption. Though administration of dilute hydrochloric acid is a popular measure to control the looseness of bowels both in addisonian pernicious anæmia[202,224] and in N.M.A. its efficacy in relieving any gastro-intestinal symptoms has been challenged[46,178].

Fever or History of Fever is a common complaint in N.M.A.[156] Usually the rise in body temperature is small—a degree or two—and irregular ; occasionally, the temperature is high and continuous. In the various series reported the frequency of this symptom has varied from about 20 to 83·3 per cent of the cases[7,12,23,28,71,92,121,122,131,136,146,156,188]. Chaudhary and Manglik[28], however, found it in only 5 out of the 27 cases of macrocytic anæmia in pregnant females. Fairley *et al.*[64] found that in their patients of N.M.A. haemolytica, fever was not a common complaint. In the few that showed small rises in the body temperature, this could be attributed either to intercurrent disease, respiratory infections, uterine sepsis etc., or, to febrile reaction following intramuscular or intravenous drug administration. It may be pointed out that the patients studied by Fairley *et al.*[64] were subjects of chronic malaria, yet fever due to recurrent malaria, was surprisingly very uncommon. Trowell[187] working in another highly malarial region—Africa—found fever present in 23 out of 50 cases of his dimorphic anaemia. Callender[18] found fever a common symptom in her cases of the so-called pernicious anæmia of pregnancy and she worked in a region where malaria is rare and almost unknown. It would, therefore, appear that fever is a common complaint in N.M.A. and this is so for both the non-hæmolytic and the hæmolytic forms of N.M.A. Further, even in the hæmolytic type it cannot be attributed to malaria. Fever is not uncommon in addisonian pernicious anaemia[202,224]. The raised body temperature in this and the related anæmias has been explained as due to mild sepsis consequent on the lowered resistance in these patients. Fairley[63], however, attributes the high rises to hæmolysis. This explanation applies apparently only to the hæmolytic variant of N.M.A. which he was describing. The rise in temperature in N.M.A. may be so mild that direct questioning alone may elicit its presence; or, as in the hæmolytic type there may be rigors or even a continuous temperature simulating enteric fever. As in the case of addisonian pernicious anæmia, in N.M.A. the fever is effectively controlled by the specific anti-anæmic therapy[156] and no special treatment is required.

Other general symptoms that may exist in severe cases of N. M. A. are anorexia, sense of tiredness, loss of vigour, breathlessness on exertion, palpitation, giddiness, throbbing in the head and neck, and attacks of syncope. In the female amenorrhœa is common; occasionally there is menorrhagia.

PHYSICAL SIGNS

In a few cases the *Loss of Weight* may be readily appreciated at a glance. Rarely it may amount to emaciation [156,169,210]. Curiously enough a marked loss in the body weight is seldom seen in the N. M. A. patients encountered in regions where malaria is highly endemic [64,72,131,210]. No explanation has been given for this behaviour. The depth of the *pallor* depends on the degree of depletion of blood. The best place to look for this pallor is the oral mucosa. The *skin* may show certain changes. Mudaliar and Narsinha Rao[130] described the skin as "modified lemon yellow" in colour. Callender[18] described it as "delicate pearly white" in her patients. Most workers have remarked that the characteristic lemon yellow skin and icteric scleræ are not found in N. M. A. [7,112,210,215]. Napier and Neal Edwards [146] and Fairley *et al.*[64] however, have noticed a definite yellowish tinge in the skin and the conjunctivæ in cases of N. M. A. which show hyperbilirubinaemia (the hæmolytic group). The skin may appear dry and rough[112,126a]. Fairley *et al.*[64] found purpura in about 25 per cent. of their patients in Macedonia; in some of the cases it was sufficiently dominating the clinical picture to suggest a primary disease process.

Pigmentation of the skin and Mucosae is not uncommon though few workers have cared to describe it. We have found it quite commonly[156]. The pigmentation affects most commonly the hands, knuckles and dorsum of the fingers. It may be more extensive and affect the dorsum of the hands and the feet, the ankle region, and even the lower one third of the legs. Not uncommonly the palms are affected. It is dark brown in colour, asymmetrical, and without any marginal zones of hyperæmia. No pruritus or pain is complained of. The oral mucosa is usually simultaneously affected -mucosa of the cheeks, sometimes of the soft palate, but seldom of the tongue. Cook[31] has described cases of macrocytic anæmia with black pigmentation of the knuckles, tongue, nasolabial folds, forehead, pigmentation around the lips, under the eyes, on the dorsum of the wrist, on the ankles and front of the legs, on the extensor surface of the legs and front of the neck. He attributed both the anæmia and this pigmentation to "a vitamin deficiency syndrome allied to sprue". Though the clinical and the laboratory data supplied prove that he was not dealing with sprue proper, there is nothing in the data put forth to differentiate the condition he is describing from N.M.A. This pigmentation in N.M.A. responds to liver therapy concomittantly with the hæmatologic response[156]; Cook's[31] experience also bears this out. *Oedema* has already been referred to above. The important *Physical signs in the chest* are enlargement of the heart and the hæmic murmurs. Hunter,[90] studying the heart in anæmia, concluded that the cardiac symptoms and signs in anæmia were in some degree independent of one another and were not directly related to the severity of the anæmia. The enlargement of the heart is due to fatty change, dilatation, or hypertrophy consequent on myocardial anoxæmia.[90,146,225]. The murmurs heard are in general due to the enlargement, and the decreased viscosity of the blood[90]. Heilig,[84] studying the heart in the anæmia of ankylostomiasis, explained the hæmic systolic murmur at the pulmonary area as due to a partial supravalvular pulmonary stenosis produced by the compression of the pulmonary artery between the dialated right ventricle and the chest wall. In patients gravely ill and in the terminal phase there may be signs of pulmonary œdema. Wintrobe[225] has described in detail the cardio-vascular changes in anæmias.

In the abdomen *Enlargement of the liver and the spleen* are the signs to be looked for in every case. Enlargement of the liver is usually moderate, in most cases producing an organ that is easily palpable. The frequency of this sign has varied in different reports from about 4.5 per cent. to 31.82 per cent. [7,18,61,78a,112,118,122]. Napier and Neal Edwards[146] noted a definite correlation between liver enlargement and severe macrocytic anæmia. Occasionally the enlarged organ is tender as well.[185,203]. Three factors have to be considered in determining the nature of the enlargement: fatty change in the organ, previous malarial infection and cardiac failure. With specific anti-anæmic therapy the organ recedes back to its normal size. Enlargement of the spleen has received more attention, chiefly because of the ætiological rôle of previous malarial infection in certain cases of N.M.A. Balfour[7] found the spleen enlarged in 18 per cent of her 150 cases. McSwiney[118] in his series of 43 patients, observed that the organ was palpable in 7 and enlarged in 3. Mudaliar and Narsinha Rao[130] were not impressed by the frequency of splenomegaly. Giglioli's[72] experience in the British Guiana, showed that splenomegaly was extraordinarily common (94 per cent) and that malaria was the cause. Napier and Billimoria,[139] and Napier and Mujumdar[145] concluded that there was a definite relationship between splenomegaly and liver-marmite deficiency in their patients. Napier,[136] later, emphasized that in his hæmolytic group of N.M.A. the spleen could always be felt as enlarged and firm but in the non-hæmolytic group it may not be palpable. Fairley *et al.*[64] had the same experience in Macedonia; in some of their patients the organ was so enlarged that together with the enlarged uterus it led to compression of the lung bases and upward displacement of the heart and predisposed the affected patients to basal collapse of the lungs and bronchopneumonia. Such marked enlargement has been recorded by others;[54,62,112] most of the workers have attributed it to previous chronic malaria. On the other hand, Callender[18] studying the so-called pernicious anæmia of pregnancy in a non-malarious zone found splenic enlargement in 30 per cent of her cases. It may be stated that splenomegaly is a common finding in N.M.A.; it may also be agreed that in regions where malaria is endemic splenomegaly would both be frequent and marked. On the other hand, splenomegaly can and does occur in N.M.A. in the absence of past or present malarial infection. This statement is supported by the observations that an enlarged spleen is a common finding in N.M.A. in non-malarial regions of the world,[126,a,168] in the so-called pernicious anæmia of pregnancy in the West,[18,202,224] and in addisonian pernicious anæmia ;[202,224]. In the last, various observers have recorded its frequency as varying from 3 to 40 per cent.[15] Whether determined by malaria or not, with adequate specific therapy the organ is considerably reduced in size, and in the non-hæmolytic cases restored to its normal size. Napier[131] and Fairley *et al.*[64] believe that chronic malarial infection produces reticuloendothelial hyperplasia in the spleen and other organs, and in the hæmolytic group of N.M.A., this hyperplasia contributes significantly to the perpetuation of the anæmic process initiated by dietetic deficiency. The enlarged organ in such cases may not completely assume its normal size.

Neurological Symptoms and Signs occupy a prominent place in the clinical manifestations of addisonian pernicious anæmia[202,224], In about 25 per cent. of the cases they may be the presenting symptoms. Both peripheral neuritis and spinal cord lesions have been incriminated as the underlying pathologic basis for the nervous disturbances[224]. Numbness and tingling in the extremities are a common symptom in N.M.A. Burning of the sole of the feet[136,156,185] and cramps of the leg muscles have also been described.[171] Diminished knee-jerks [64,136] and extensor planter response[185] have been recorded in a few cases, but loss of motor function and loss of any form of sensations have not been met with.[38,136,138 185]. Deficiency of some factor of the vitamin B complex and ischæmia of the spinal cord have been held to play a part in the causation of these paræsthesias[108]. Absence of subacute combined degeneration of the cord in N.M.A. had been held hitherto as a point of distinction between this anæmia and addisonian pernicious anæmia. In the Indian prisoners of war suffering from N.M.A. Walters Rossiter and Lehman [198] described three kinds of neurological disturbances: 1) peripheral neuritis (beriberi) reacting to vitamin B_1 administration, 2) "captivity cord syndrome" showing either sensory ataxia due to involvement of the posterior columns or spastic paraplegia from pyramidal tract degeneration ; both these were not accompanied by achlorhydria or constant changes in the blood picture, and the ataxic group reacted to treatment but the spastic cases did not, 3) "captivity amblyopia" which recovered with a high protein high caloric diet. Degazon's[53] case reported from Belize, British Hondura, is the only solitary record of subacute combined degeneration of the cord in N.M.A. reported in the literature up to date. The patient was a coloured pregnant woman aged 22 showing marked loss of power in the upper and lower limbs, and, diminished sensations of pain and touch on the inner aspects of legs. The sense of position was impaired in the upper limbs and in the left leg. The abdominal reflexes and the knee and ankle jerks were lost; the plantars could not be elicited. Blood examination showed a macrocytia anæmia (M.C.V. 128.5 u 3). Free hydrochloric acid was found in the gastric juice. She was treated with liver extract parenterally, and hydrochloric acid by mouth; vitamin B_1 was given simultaneously. Though she felt better there was no improvement in her neurological condition. She gave birth to a premature baby, and, after that, her symptoms subsided gradually, enabling her to walk in a month's time. She had been followed for about 21 months at the time of the report and there had been no recurrence of the symptoms.

Considering the clinical manifestations of N.M.A., and comparing them with those of other megaloblastic anæmias, especially addisonian pernicious anæmia, it may be concluded that no symptom or sign is specific for N.M.A. A diagnosis cannot be made on the clinical features alone. In every case a proper hæmatological investigation is imperative.

HAEMATOLOGICAL FINDINGS

I) *Cytology:* Enumeration of the red blood cells and estimation of the hæmoglobin show that both are depleted to a variable degree, but the former being more affected than the latter, the anæmia is usually a macrocytic one. Red cell counts below a million per c. mm. are not uncommon,[64,105,118,122,156,215] and, in pregnant cases nearing the term, are of grave omen. Both in males and females, it is surprising to find how with such marked deterioration of the blood the patients look outwardly so well, and may even enter the hospital walking[215].

In uncomplicated cases and especially in the severe ones, there is usually a leucopenia[18,64,105,136,151,168,182,215]. In pregnant females the leucocyte count may be within the normal range[105]. Napier[136] found leucopenia in non-pregnant hæmolytic cases but usually not in pregnant patients or the non-hæmolytic cases. Fairley *et. al.*[64] found leucopenia in both hæmolytic and non-hæmolytic forms and their patients were mostly pregnant females. In post-partum cases and in those with some form of sepsis there may be leucocytosis.

The platelets are decreased during the active stage [64,105] and Fairley *et. al.*[64] have reported thrombocytopenia with purpura in 25 per cent. of their cases. In 14 cases the platelet counts varied from 5,400 to 163,000 per c. mm., the average being 66,915 per c. mm. In some of these with very low platelet counts purpura dominated the clinical picture. Callender[18] and Kothari and Bhende[105] have similarly observed low platelet counts in their patients but not purpura. Both leucopenia and thrombocytopenia improve with specific anti-anæmic therapy.

A standard technique should be employed for the preparation and staining of the blood smears[184,187]. In the leucopenic cases the differential count shows an inversion of the normal neutrophil-lymphocyte ratio[64,215]. Napier[136], however, found that in his cases without leucopenia, the distribution of the different leucocytes did not differ markedly from the normal. In cases showing leucocytosis the neutrophils may be present in normal numbers or may be even increased. Some observers have noted a shift to the right in the neutrophil series and an Arneth count typical of addisonian pernicious anæmia[18,130]. Napier[136] has, however, denied this. Presence of eosinophils above the normal figure of 3 to 4 per cent. should prompt a meticulous search for parasitic ova in the fæces, as in endemic zones N.M.A. may be complicated by ankylostome infection[9,54,105,115,182,189].

To obtain detailed information about the morphology of the blood in N.M.A., Trowell[184,187] has emphasized examining a properly prepared smear carefully—its edges, its centre and its tail end. Macrocytosis, if marked, is easily detected in the smear with some experience ; according to Trowell[184], the macrocytes tend to collect at the edges and the tail end of the smear. Macrocytosis, if moderate, may be missed in the smears[224]. Determinations of the mean corpuscular volume and/or the Price-Jones curve are more sensitive indicators of the red cell size. Though the majority of the case of N.M.A. show macrocytosis, normocytosis[136] or even microcytosis[18,156] does not rule out the diagnosis of nutritional megaloblastic anæmia. Oval macrocytes, megalocytes, are present in moderately advanced cases. The red cells, unlike those in addisonian pernicious anæmia, do not, in the smear, give an impression of being stuffed with hæmoglobin. Anderson and Roberts[4], on the other hand, found target cells in 4 out of their 5 cases of N.M.A. Anisocytosis is present but many authors[136,182,215] have opined that it is not as marked as in addisonian pernicious anæmia. Others have found it constantly, and, according to them, its degree varies with the severity of the anæmia[4,14,51,64,121,168,184,198]. Trowell[184,185,187] was so impressed by its presence in every case that he preferred to call N.M.A. as encountered in Africa, "dimorphic anæmia." Poikilocytosis is, however, not marked unless the red cell count is below a million per c.mm[64,136,159,215]. Mudaliar and Narsinha Rao[130] found it constantly, even in the less severe cases. In any case, absence of marked anisocytosis and poikilocytosis in N.M.A., though often emphasized, should not be taken as points of distinction from addisonian pernicious anæmia.

In the non-hæmolytic cases, polychromatophilia is never marked ; it may appear during treatment[64,136,215]. Polychromatophilia may be present in the hæmolytic cases[64,136,215]. Basophilic stippling, Cabot's rings and Howell-Jolly bodies may be seen in severe cases, as in any severe anæmia. The red cells, in contrast to addisonian pernicious anæmia, may show hypochromia, even vacuolation. Such cells tend to collect in the centre of the smear and their presence indicates coexistent iron deficiency[184,187]. A better criterion to detect iron deficiency is of course, estimations of mean corpuscular hæmoglobin concentration and the saturation index. Nucleated red cells are present in the peripheral blood in moderately advanced cases. The prevalence of normoblasts is admitted unanimously[7,64,78a,105,129,130,136,156,183,184,185,198,215] ; this is even more so for the hæmolytic group[61]. On the occurrence of megaloblasts in the peripheral blood opinion seems to be divided. In view of the lack of any clear definition of the "megaloblast" at the time some of these series were reported, and, in the absence of any of these authors having made an attempt to define his or her " megaloblast," the divergence of views is not difficult to appreciate. Balfour[7], Chaudhary and Manglik[28], Fairley *et al.*,[64], Russell[159], Trowell[illegible], Moore *et al.*[126a], Callender[18], Spies[163], Spies *et al.*[171], Kothari and Bhende[105] etc. found the megaloblast quite frequently. McSwiney[118], Mackie[illegible], Wills and Mehta[215], Wills[203], Mitra[122,123], Gupta[78a], Mudliar and Menon[129], Mudliar and Narsinha Rao[130], Das Gupta and Chatterjea[38] observed that megaloblasts were seen occasionally and normoblast always preponderated. Napier[131,136] stated that in N.M.A. he had never seen the typical hæmoglobinised megaloblast in the peripheral blood though he had seen " the basophilic megaloblast that occurs in normal bone marrow." Callender[18] found the typical Ehrlich's hæmoglobinised megaloblast (pathologic) quite commonly in her pregnant patients while Kothari and Bhende[105] found that the megaloblasts (pathologic) in the cases studied in Bombay were always basophilic. The original concept of the presence of a megaloblast in the normal bone marrow propounded by Doan, Cunningham and Sabin[55] has been now almost universally abandoned and most authorities[94,99,183,185,202,221], at the moment, believe that megaloblasts and their products are functionally as well as structurally abnormal, and, that the presence of megaloblast in the peripheral blood or in the bone marrow indicates a dysplastic marrow. The significance of this change in the outlook has to be grasped thoroughly as the diagnosis of certain cases of anæmia, due to the deficiency of the liver principle, may depend entirely on the demonstration of a true megaloblast in the peripheral blood or the bone marrow, (Segerdahl[161], Stevenson[172], Davidson *et al.*[11], Callender[18], and Kothari and Bhende[105]) irrespective of the other attributes of the blood-picture like macrocytosis. Thus Callender[18] found the presence of a true megaloblast in the peripheral blood as a valuable aid in diagnosis in 13 out of her 25 cases of the so-called pernicious anæmia of pregnancy and Kothari and Bhende[105] studying N.M.A. in pregnant females in Bombay, had the same experience in 15 out of their 45 cases. Though, upto date, cases have been described only among the pregnant females[18·44·67·105·161·172], it is possible, even probable, that similar cases exist in the non-pregnant females and males (cases of N.M.A.), and, owing to a none-too-thorough an examination are being missed. According to most of the workers an average uncomplicated case of N.M.A. shows a low reticulocyte count[14·64,105·131·136·141·182·183·–185·215]. In the hæmolytic group of N.M.A. the reticulocytic count may be high[64,131,136,146], (5 to 20 per cent.); very high figures are, however, never encountered as the co-existent nutritional deficiency damps down the response of the marrow.

II). *Colour Index, Mean Corpuscular Hæmoglobin and Volume Index:*— In an average uncomplicated case of N.M.A. the figures for these three values are usually higher than the normal range[166·167] and *suggest* the presence of macrocytosis. It is necessary to emphasize that figures falling within the normal limits do by no means indicate that macrocytosis is absent. Estimation of the colour index (C.I.) features in every report and a C.I. above unity has been considered an important characteristic by almost every worker[14,28,64,105,126a,129,130,136,158,163,203,212,215]. Some authors, however, have included, apparently under the name N.M.A., cases of anæmia with C.I. of 1, or, even less than unity. Such cases have been described both in the males[12] and the females but especially in the pregnant females[7 28,64,78a,122,123,129,130,159,203,215]. Most of them have not mentioned the standard employed for the hæmoglobin estimation and in the absence of the other criteria -the presence of the megaloblast in the peripheral blood or the marrow, or, a specific response to marmite or liver therapy--many of the cases are not admissible as cases of N.M.A. The C.I. is lowered during specific treatment and may become less than unity[131,215]. In cases treated partially, if they do not give a proper history, a low C.I. is, therefore, apt to mislead those who would rely solely on this value for the diagnosis. The mean corpuscular hæmoglobin (M.C.H.) is increased in most of the cases; this value has the same significance and the same disadvantages as the C.I., as far as the inferences regarding the red cell size are drawn from its determination. Few reports mention the values for the volume index (V.I.); the V.I. is usually raised[14·105].

III). *Mean Corpuscular Volume, Mean Corpuscular Diameter and Price-Jones' Curve* :—The mean corpuscular volume (M.C.V.) is the most sensitive indicator of the red cell size except when spherocytosis is present[224]. Its sole disadvantage is that it gives information regarding only the average size of the cell. In N.M.A. the M.C.V. is characteristically raised. The values for the normal range have been worked out by many workers in different parts of India;[139,143,145,166,167], figures are also available for normal pregnant females [139,146]. When all these figures are considered in relation to the standard deviation (wherever the latter value has been calculated) the normal range becomes very wide and it is well nigh impossible to lay down absolute figures for the range within which all normals could be accommodated. Wintrobe[222] has stated categorically that the probability of a M.C.V. of 95 μ^3 representing macrocytosis is 49 : 1, whereas, if it is 99 μ^3 the probability is raised to 1999 : 1. A figure for the M.C.V. above 95 μ^3 should, therefore, be viewed with extreme suspicion. The raised M.C.V. in N.M.A., according to various reports, has ranged from 96 to 170 μ^3 [14, 28,64,105,121,185,187] ; in most of the cases, however, the rise is moderate[18,64,105,131,136,184,185,187]. What is more important, a normal M.C.V. does not negative the diagnosis of N.M.A.[18,105]. Napier[136,144] has reported several cases with normal M.C.V. Chatterjee[24] explained the raised M.C.V. as due to increased red cell thickness as it was not invariably associated with an increased mean corpuscular diameter. A M.C.V., lower than than normal, may even be compatible with the diagnosis of N.M.A.[67]. In 4 out of 12 cases of her pernicious anæmia of pregnancy, Callender[18] found the M.C.V. within the normal range. Kothari and Bhende [105] had a similar experience in 3 out of 45 cases among pregnant females and in 2 cases the M.C.V. was well below the lowest figure for the normal range. The mean corpuscular diameter (M.C.D.) in N.M.A. is similarly increased. Direct measurements have shown that the value is not very high, the figures in various reports falling at the upper level of the normal range or slightly higher[18,105,131,136,184,185,187]. Fairley *et al.*[64] found that in the non-hæmolytic group of N.M.A. the M.C.D. was significantly raised above the normal limits, but, in the hæmolytic cases they were surprised to find that, in a number of cases, there was a high M.C.V. but the M.C.D. indicated normocytosis or only slight macrocytosis. Trowell[184,185,186] found that in most of his cases of dimorphic anæmia the M.C.D. was mostly at the upper level of the normal range and he opined that estimations of the M.C.D. and the C.I. were of limited value in N.M.A. Trowell,[184,185] like Fairley *et al.*[64], was working in a highly malarious region and dealing mostly with N.M.A. hæmolytica. Callender[18] studying her pernicious anæmia of pregnancy in an entirely non-malarious zone observed that the M.C.D. varied from 6.89 μ to 8.98 μ; in the majority of instances it was within the normal limits and in 6 it was less than the normal mean of 7.2 μ. Kothari and Bhende[105] in a series of 45 cases found that in 19 the M.C.D. was between 7.263 and 8.189 μ; in 16, between 6.888 and 7.592; and, in 10 between 6.368 and 7.0728 μ. In all these patients the sternal marrow was megaloblastic. Not many studies are available for a detailed analysis of the Price Jones curve (P. J. curve) in N.M.A. Napier [131,136] stated that even when the P.J. curve was shifted to the right there was not much flattening. Callender[18], dealing with pernicious anæmia of pregnancy, remarked that even in severe cases a curve may be found which closely approximated to the normal and that macrocytosis may be entirely absent. Kothari and Bhende [105], dealing with pregnant females, found that the values for the standard deviation and the coefficient of variation were much below those usually encountered in addisonian pernicious anæmia. Callender[18] had the same experience. This last point is of some significance because Darland Heath and Minolt[33] have claimed that below the level of 2,500,000 red cells per c. mm. the degree of anisocytosis, as revealed by the standard deviation and the coefficient of variation of the red cell diameter, serve as a fairly accurate criterion for the diagnosis of addisonian pernicious anæmia from many other types of macrocytic anæmias. It would appear that the results obtained with the P.J. curve in N.M.A. have proved somewhat anamalous. Especially the discrepancy between the M.C.V. estimated by the hæmatocrit and the M.C.D. determined from the P.J. curve has not been satisfactorily explained, and, a further study of the P.J. curves in non-hæmolytic and haemolytic N.M.A., in males, non-pregnant females, and pregnant females is warranted.

IV). *Spherocytosis:* The discrepancy between the high values for the M.C.V. and the normal or only slightly raised M.C.D. has suggested to some[11,24,136,185], the occurrence of spherocytosis or macrospherocytosis in N.M.A. Trowell[185] could detect spherocytes even in stained smears in his material of dimorphic anæmia. Few workers have measured the mean corpuscular average thickness (M.C.A.T.) to demonstrate unequivocally the presence of spherocytosis. Fairley *et al.*[64] found that out of 7 cases of hæmolytic N.M.A., in 1 the M.C.A.T. was below the maximal normal value of 2.5 μ, in 1 it equalled this value, and, in 5 cases the M.C.A.T. exceeded the maximal figure. Chatterjee[24] and Trowell[186] finding the cell thickness increased believed that a case had been made for the existence of macrospherocytosis in at least some cases of N.M.A. Kothari and Bhende[105], in a series of 45 cases of N.M.A. in pregnant females found the maximum and the minimum limits of M.A.C.T. to be 2.771 μ and 1.580 μ respectively and the average M.A.C.T. was 2.143 μ. The values for the $\frac{\text{M.C.D.}}{\text{M.A.C.T.}}$ ratio ranged from 4.142 to 2.630 : 1 (normal range 4.2 to 2.4 : 1). These results do not support existence of definite spherocytosis.

V). *Mean Corpuscular Hæmoglobin Concentration, and the Saturation Index :* Trowell's[184,185,187] concept of dimorphic anæmia --indicating a dual deficiency of iron and liver principle--and his demonstration of the prevalence of this form of anæmia in regions where malnutrition is common have clearly brought out the importance of estimating the mean corpuscular hæmoglobin concentration (M.C.H.C.) and the saturation index (S.I.) in every case of N.M.A. The former being an absolute index is more reliable than the latter. Though Trowell[184, 185,187] contended that this dual deficiency could be easily recognised from the dimorphic picture seen in the peripheral blood smear, a raised M.C.V. with a low M.C.H.C. would be a more dependable pointer for the inexperienced. Stated in other words, the problem is to decide whether the macrocytic anæmia under consideration is orthochromic or hypochromic. Whether microcytosis or normocytosis associated with a megaloblastic marrow should suggest a dual deficiency has not been answered in clear-cut terms, though, probably this may be so. Cases of N.M.A. in which macrocytosis (raised M.C.V.) was associated with hypochromia (low M.C.H.C.) have been recorded by many observers in this country[12,14,28,81,105,123,129,130,131,136,144 .146,156,181]. Even outside India they are not uncommon.[18,56,64,184,185,187,197]. It must be emphasised though, that barring Trowell[181,185,187] none of these authors have demonstrated in their cases a double reticulocyte peak, first to the administration of the liver principle and next to the administration of iron, or *vice versa*.

VI). *Fragility of the Erythrocytes :* The possibility of the existence of spherocytosis in N.M.A. naturally prompted workers to determine the fragility of the erythrocytes. Evans and Wills[59], in a series of 40 cases found that the uncorrected median corpuscular fragility (M.C.F.)—concentration of salt solution which produced 50 per cent. hæmolysis—lay between 0.255 and 0.375 per cent. of sodium chloride with a mean of 0.315 per cent. The normal mean with the same method was 0.366 per cent. If corrected for anæmia, the range became 0.302 to 0.428 per cent. with 0.356 as the mean: and if the males and the non-pregnant females were excluded, in the rest the figures were significantly higher than for the normal persons. The results indicated that pregnancy by itself caused increased fragility masking the decrease which takes place in uncomplicated N.M.A. There was no relationship between the degree of anæmia and the M.C.F. figures[59]. Fairley *et al.* [64] found that in N.M.A. in the pregnant females the qualitative corpuscular fragility test was normal. Elliot[56] showed that there was a significantly raised M.C.F. in the so-called pernicious anæmia of pregnancy and he considered that this was a differentiating characteristic not present in "other anæmias associated with pregnancy." It is necessary to add that according to Elliot[56], the common form of anæmia of pregnancy in India (T.M.A.) is not the same as the pernicious anæmias of pregnancy, but merely an anæmia associated with pregnancy. Callender[18] found that in 3 cases the M.C.F., after correction for anæmia, was either normal or diminished; same was the experience of Miller and Studdert[121]. Kothari and Bhende[105], in their series of 45 cases of N.M.A. in pregnant females found that the uncorrected figures for 95 per cent. hæmolysis varied from 0.40 to 0.26 per cent. of sodium chloride. Davidson and Fullerton[46] remarked that spherocytosis without increased corpuscular fragility was a finding common to dietetic anæmias (macrocytic), anæmias of pregnancy, and anæmia of idiopathic steatorrhea.

It would appear that in N.M.A. the blood picture is very variable. The anæmia is usually macrocytic, but neither normocytosis nor microcytosis exclude its existence. This statement has no relationship to the fanciful claims made by Chatterjea and Basu[26], Hare[80,82], Mudaliar and Menon[129], etc., that in the so-called anæmia of pregnancy the anæmia goes through a regular cycle of stages—normocytic →microcytic →normocytic and hypochromic macrocytic—depending on a pathological cycle in the marrow consisting of regeneration, compensation, and bone marrow failure. These claims are not warranted by the evidence put forth. Contrast these variable blood pictures in N.M.A. with that encountered in addisonian pernicious anæmia as expressed by Haden's[79] dictum "A diagnosis should never be made of pernicious anæmia in the absence of macrocytosis of the red cells." Among the abnormalities pertaining to the red cells, the presence of a true megaloblast in the peripheral blood is the most important diagnostic feature. Usually there is a low reticulocyte count, leucopenia, and, a low platalet count. Determination of the M.C.V. and M.C.H.C. should be practised as a routine to detect the presence of a dual deficiency of the liver principle and iron.

THE BONE MARROW

The marrowgram in normal Indians has been worked out by Napier and Sen-Gupta[147], and Bhende[13]. Three pertinent questions may be asked about the changes in the marrow in N.M.A.: 1) What is the general appearance of the marrow? 2) Are there any changes in the marrow exclusively specific to N.M.A. ? and 3) How does the marrow react to specific treatment ? The earlier observations on the marrow were confined to *post-mortem* studies, and, apart from the defective material available for study, they did not proclaim clearly what they really meant. Thus Balfour[7] studying 2 cases at autopsy, noted that in 1st with a C.I. of 2.0, the marrow contained large aplastic areas, nucleated red cells were few, and that the few cellular islets present were composed of large megaloblasts (not defined) and eosinophil myelocytes ; in the 2nd autopsy on a patient with a C.I. of 1.3, the marrow showed some aplastic areas but in between it was cellular with a number of mitotic cells. Mitra[122] examined the marrow in 4 cases at autopsy ; in 3 the tibial marrow was aplastic but in the 4th case the marrow was hyperplastic with plenty of megaloblasts (not described). Gupta[78a], in 4 cases studied at autopsy, found the marrow hyperplastic in all; the hyperplastic marrow consisted of " myeloid cells —mostly non-granular mononuclears". Wills and Billimoria[211] studying the marrow of a monkey in which they thought they had reproduced N.M.A. (T.M.A.) experimentally by diet, opined that the marrow was megaloblastic. Though they had no opportunities to study this in human cases they assumed that in 'N.M.A.' in the humans the marrow must similarly show megaloblastic hyperplasia. Their illustrations of the monkey marrow were not satisfactory and Trowell[187] pointed out that in Turnbull's opinion the most characteristic feature in the marrow of monkey in which Wills[207] had induced N.M.A. was the change in the leucocytic cells, namely, hypersegmented neutrophils and giant metamyelocytes and premyelocytes. With the popularisation of the sternal puncture technique, the marrow was examined more frequently and its cytology studied in detail. Napier and Majumdar[145] did not encounter any " megaloblasts " in the sternal marrow in their 19 cases of liver-marmite deficiency anæmia ; the red cells series, in these, was made up of " erythroblasts," varying from 5.5 to 19 per cent and normoblasts varying from 13 to 44 per cent. of the nucleated cells. In the same year, in another report, Napier *et al.*[144] describing the marrow changes in 8 cases observed that the megaloblasts varied from 0·5 to 28 (no megaloblasts in 1 case), erythroblasts from 2 to 19.2, and normoblasts from 17.5 to 67.5 per cent. of the nucleated cells in the sternal smear. Napier[136], giving further details of the marrow changes, stated that the red cell elements were distinctly increased and there was also a marked increase in the (normal) basophilic " megaloblasts " at the expense of the more mature normoblasts ; further, he had rarely seen a hæmoglobinised megaloblast (pathologic) in the marrow of N.M.A. Thus the bone marrow reaction was different from that seen in addisonian pernicious anæmia ;

in N.M.A. there was a general hyperplasia of the red-cell-forming elements with excessive multiplication but delayed maturation at the megalo-erythroblastic, level and, therefore, the effect of the deficiency was shown a little later in the life of the maturating red cell than in addisonian pernicious anæmia--" an anaplasia rather than dysplasia ". In the 5 cases detailed in this report the " megaloblasts " (normal) formed 3.5 to 17.7, the " erythroblasts " 1 to 7.5, and the normoblasts 7.4 to 59.5 per cent. of the nucleated cells. In his review of " anæmia of pregnancy in India " Napier[137] reiterated his former conclusion: " the majority showed normoblastic hyperplasia and in no case was there typical megaloblastic hyperplasia that one sees in pernicious anæmia (addisonian), but in a few cases there were a few megaloblasts (normal) and a high percentage of erythroblasts." This view is apparently shared by some even up to this day[75], [182].

Fairley *et al.*[64] have given detailed description of the marrow in N.M.A. as seen in Macedonia. There was a general hyperplasia of the marrow elements with increase in the number of hæmocytoblasts, promegaloblasts and proerythroblasts. Basophilic and polychromatic erythroblasts were present but not orthochromatic ones; ripening sufficient to produce a really pink cytoplasm in a cell with finely stippled nucleus was a rarity. Mitosis in the red cell precursors was seen quite frequently. There was a combined megaloblastic and normoblastic type of erythropoiesis suggesting that the failure of maturation of the megaloblasts accounted for part of the pathologic changes and abnormal activity in the marrow. Equally characteristic was the alteration in the neutrophil precursors—precocious nuclear polymorphism, atypical eosinophil, amphophil and azure granules, cytoplasmic vacuolation and splitting of the nucleus. There were giant metamyelocytes with elongated band-shaped nuclei which contained holes and areas of rarefaction. The mature neutrophils also showed hypersegmentation and holes in their nuclei. The megakaryocytes were scanty and had a small quota of cytoplasm. In short there was a panmyelopathy, hyperplasia that was functionally ineffective—" a frozen hyperplasia "—and the authors posed a question whether all these changes were the result of the affection of the hæmocytoblast, the stem cell, or, the reticuloendothelium of the marrow, as suggested by Jones[99] for addisonian pernicious anæmia.

At this stage, it is necessary to point out that Napier and his co-workers[131], [132], [134], [136], [137], [144] were employing the old terminology of Doan Cunningham and Sabin[55]. These authors' thesis that the megaloblast is the first differentiated precursor of the red cell series derived from the reticuloendothelial cell is, by now, universally discarded ; the megaloblast (at least in the extrauterine life) is to most workers a pathologic cell not present in the normal marrow. And with this re-orientation of view the term "erythroblast" should connote a generic name applied to any nucleated red cell. The point must be clearly grasped because "the revivified megaloblast has a definite message for the clinician. A marrow showing megaloblastic hyperplasia is a sign that liver treatment should be given and that good response may be expected in the majority of patients[107]. The megaloblasts encountered by Napier and his co-workers may have been hæmocytoblasts, proerythroblasts or pro-megaloblasts. Many of their megaloblasts were probably pathologic cells—the products of a dysplastic marrow—as the 'megaloblasts' of Fairley *et al.*[61] certainly were, as far as can be inferred from the description of these cells.

Trowell[185-187] has described in detail the marrow pattern in his cases of dimorphic anæmia. He[184] emphasized the value of correct staining of the sternal marrow smear, lest artifices be produced in the chromatin structure of the erythroblasts, thus making the distinction between megaloblasts (pathologic) and normoblasts difficult. In general, in his dimorphic anæmia, the marrow pattern was a mixture of megaloblastic and normoblastic developments[184]. He deprecated the zeal for rigid classification of cells into different categories because in many cases the recognition of individual cells was merely a matter of opinion[184]. He believed that deficiency of the liver principle operated at all the stages of the development of the red cells and not just at one stage (a belief that finds some support in the work of Jacobson[97]), while iron was similarly necessary for the development of hæmoglobin and eosinophilia in the cytoplasm of the red cells and their precursors. The two changes were largely complimentary : liver principle produced nuclear maturation and its absence produced in the red cell series a shift to the right (cytoplasmic ripening present) ; iron was essential for cytoplasmic development and its deficiency led to a shift to the left (nuclear maturation accelerated compared to cytoplasmic ripening). With this dual deficiency present in his dimorphic anæmia, he found that the marrow showed increased cellularity with a predominantly normoblastic erythropoiesis (deformed—normoblasts described by Bodley-Scott[16] may be present) and megaloblasts and proerythroblasts could be found only at the tail end of the smear ; senile neutrophils and pathologic large metamyelocytes were usually but not always present. To this mixture of normoblastic and megaloblastic developments existing side by side Davis and Davidson[51] have applied the term "dimorphic marrow" as the most appropriate. In Trowell's [184] opinion, it is absurd to publish differential cell counts on sternal smears as all three types of erythropoiesis are usually present myeloid, normoblastic and megaloblastic. Though it may be admitted that because of the normal range of variation and the difficulty of differentiating precisely every premature cell in the marrow only gross changes in the marrow pattern are significant, such a statement may not be conceded by all morphologists. Callender[18] has described the marrow changes in detail ; in the great majority there was a mixed megaloblastic-normoblastic reaction with presence of multinuclear and giant forms of megaloblasts. Presence of pathologic leucocytes was constant. According to her, the presence of megaloblasts in the marrow is the most important criterion for the diagnosis of the pernicious anæmia of pregnancy. Zuelzer Newhall and Hutaff[226] studying the marrow in what they call " the megaloblastic anæmia of infancy," describe similar changes in the marrow. They also describe an " intermediate cell "—a cell morphologically occupying a position midway between the typical megaloblast and a typical normoblast as another characteristic component of the marrow. In 7 of their 15 cases this was the predominant cell in the marrow, in addition to the classic megaloblast. These workers believe that the intermediate type of erythropoiesis is an early stage of megaloblastic transformation. According to the same authors, abnormalities of the leucocytes—hypersegmented neutrophils, giant metamyelocytes and premyelocytes—are the earliest changes in megaloblastic conversion ; in 2 of their 15 cases the marrow showed this change plus a normoblastic reaction and these patients reacted to folic acid therapy in the same manner as the ones that had a full blown megaloblastic marrow pattern. Davidson, Girdhood and Innes[49] have described marrow cells intermediate between megaloblastic and normoblastic in some cases of sprue, and Dacie and White[32] believe they have seen lines of cell development in the marrow, morphologically lying between the normal adult pattern and that known as megaloblastic in a variety of conditions, including sprue.

It is obvious that the problem is already showing signs of getting more and more complex. Leaving to the morphologists to fight out the complex issues involved, the practicing physician may, at the moment, remain contented with the established fact that every case of N.M.A. shows a mixed megalo-normoblastic reaction in the marrow. This dimorphic ap-, pearance of the marrow pattern, though pointed out by Trowell[184,185,187] can be recognised in the earlier reports[64,136,144,145,192]. Even now the marrow in N.M.A. continues to be described as megaloblastic[37-38,64,75,136,414,145,168,185,187]. The expressions "megaloblastic" or predominantly megaloblastic" have never been defined. This does not matter much because to most the unequivocal demonstration of even a few megaloblasts would suggest a dysplastic marrow due to deficiency of the anti-anæmic principle, however brought about[94]. Contrariwise, so long as the anti-anæmic principle is normally available, demands for increased red blood cells, whatever their cause, are met by proliferation of the normoblastic series of cells[93,94]. In uncomplicated chronic malaria the marrow is normoblastic[61]. It may again be emphasised that it would be unjustifiable to deduce the megaloblastic state of the marrow from the presence of macrocytosis in the peripheral blood[45].

The marrow changes described above, resemble very much those found in addisonian pernicious anæmia[34]. Is there any difference at all between the two? Both show megaloblastic erythropoiesis, monstrosities of the leucocytes and depletion of the megakaryocytes—a panmyelopathy. In both normoblastic erythropoiesis is proceeding side by side. Both react to specific therapy in an identical manner. Some workers have pointed out that in contrast to addisonian pernicious anæmia, in N.M.A. the megaloblasts are present in smaller numbers and that Ehrlich's hæmoglobinised megaloblasts are either absent or present in very small numbers[12,14,37-39,75,105,121,136,144,145]. Both the criteria are not absolutely dependable. The number of megaloblasts in the marrow—as expressed in per cent. of the total nucleated cells—varies according to the severity of the anæmic process[34]. Previous treatment may also affect the picture[34]. Besides a number of factors—from the amount of marrow withdrawn by the puncture to the method of staining and scrutinising the smears of the material—may alter the distribution of the various cells and may make the quantitative estimations less real than they appear at first sight. On the second point it may be agreed that though cases of N.M.A. in which hæmoglobinised megaloblasts are present in the marrow have been reported[67], on the whole this cell is very infrequently encountered in N.M.A.[63,66,183,192]. The matter is not, however, so simple. Thus, Rohr[158] and Segerdahl[161], in attempting to distinguish the marrow changes in pernicious anæmia of pregnancy from addisonian pernicious anæmia, observed that in the former there was a more mature type of erythropoiesis with fewer promegaloblasts and basophilic megaloblasts and relatively more ripe orthochromic forms. Callender[18] had a similar experience in one of her cases. Trowell's[184] experience, on the other hand, was exactly the opposite; in his opinion the megaloblasts of addisonian pernicious anæmia always showed a nucleus that was reticular and had a more primitive chromatin network and yet a more eosinophilic cytoplasm than the megaloblasts of N.M.A. It would seem that the majority of the workers support Trowell's[184] opinion. Probably the co-existant iron deficiency in N.M.A. may account for this difference in the cytoplasmic structure of the megaloblast.

THE GASTRIC JUICE

There is no evidence that normally the gastric acidity in Indians differs from that in the Europeans[137,143]. There is a general consensus of opinion that in N.M.A., in contrast to addisonian pernicious anæmia, free hydrochloric acid is usually present in the gastric juice[4,9,12,11,18,28,37,38,64,102,105,130,131,136,142,156,168,184,185,187,203,205,210-212,215]. The acid content is, however, diminished and some degree of hypochlorhydria is a constant finding[12,14,64,71,105,130,131,136,156,168,176,177,185-187,210 215]. A few cases may show hyperchlorhydria. It is necessary to emphasize, however, that the absence of free hydrochloric acid in the gastric juice, even after histamine stimulation—a histamine-fast achlorhydria (true anacidity)—is no evidence against the anæmia being N.M.A.[12,14,28,37-39,44,62,117,126a,130,156,163,171,181,187] though its presence is evidence for it in differentiating N.M.A. from addisonian pernicious anæmia. Napier[136] felt that the incidence of histamine-fast achlorhydria in N.M.A. was the same as in the general population but the observations of McRobert, Govind Reddy and Subramaniam[117a], Bhende [12], Bhende and Patel[14], Das Gupta and Chatterjea[38], etc., would seem to indicate a higher frequency. Examination of the protocols of various reports gives the same impression[39,44,156,181,214]. The histamine-fast achlorhydria in N.M.A. may be recovered from after treatment and free hydrochloric acid secreted again[42-44,61,117a,181]. Connery and Jollife[30] have recorded recovery of free acid after treatment even in a case of addisonian pernicious anæmia with subacute combined degeneration of the cord; the authors encountered 2 such cases previously described in the literature. Moore *et al.*[126a] noting intermittent achlorhydria in their patients of N.M.A., contended that at least some of the cases described in the literature as addisonian pernicious anæmia with free hydrochloric acid in the gastric contents may have been really cases of N.M.A. On the other hand, cases of N.M.A. with histamine-fast achlorhydria may have been called pernicious addisonian anæmia. Such findings emphasize the pitfalls of relying on a single test for diagnosing any disease process. Usually the achlorhydria in addisonian pernicious anæmia is permanent, irrecoverable and uninfluenced by any treatment [202,224]. The basis for the common hypochlorhydria or the occasional achlorhydria in N.M.A. cannot be stated with certainty. Hellstrom *et al.*[87], found that achlorhydria was more than three times as common in persons subsisting on an unvaried lactocereal diet deficient in vitamin B complex, compared to those taking a larger variety of foodstuffs. Berry[9] found chronic atrophic gastritis common in patients living on inadequate diet and that administration of liver extract, vitamin B_1 complex and improved diets produced strong symptomatic improvement with disappearance of the atrophy. Wills[208] suggested that vitamin B_1 deficiency may be the causal factor in achlorhydria. Anæmia *per se* may also lower the level of the gastric acidity[3,5]. Achlorhydria has, of course, no aetiological significance even in addisonian pernicious anæmia beyond causing some diminution in the absorption capacity of the gastro-intestinal tract[8,153,193,202,221]. No studies are available in this country, regarding the presence, diminution or absence of the intrinsic factor in the gastric juice in uncomplicated N.M.A. This is because the test for the intrinsic factor is a biological one and the test animal is an untreated case of addisonian pernicious anæmia; the latter is so uncommon in the tropics. It is presumed that the intrinsic factor is present in normal amount. In the so-called pernicious anæmia of pregnancy Strauss and Castle[175,177] have demonstrated diminution in the amount of intrinsic factor secreted and have pointed out its aetiological significance. In complicated N.M.A. anaemias of sprue and pellagra, in some cases, the intrinsic factor has been found to be absent[126a]. Wills[203] stated that there was no failure of gastric function in N.M.A. but in view of the observations of Strauss and Castle[175] in pregnant females that the intrinsic factor may diminsh even in the presence of free acid, the statement warrants a proof by actual observations. The morphological changes in the gastric mucosa in N.M.A. will be discussed under the post-mortem findings.

THE FAECES

In N.M.A. the fæces are usually normal[64,188,210,215]. In diarrhœic cases the fæces may be watery. Cook[31] and Chaudhari and Rai Chaudhari[27] have described a sprue-like condition among the civilians in this country; there was macrocytic anæmia and diarrhœa but without any increased fat excretion. Fairley *et al.*[64], in their series of N.M.A. in Macedonia, found that the fat content of the fæces was low with a normal ratio of split to unsplit fat; with the low content of fat in the diet of a poverty-stricken population this would be expected. Not many studies giving information on the urobilinogen excretion in the fæces are available; in the hæmolytic group it may be increased. Stimulated by Hurst's[91] suggestion that in addisonian pernicious anæmia the achlorhydria (with the consequent loss of the sterilising power) may produce abundant multiplication of the intestinal flora, some authors[130] in the early studies, attempted cultures of the fæces to demonstrate excessive activity of the normal flora of the intestine or the presence of abnormal flora. The results were not conclusive and the thesis would seem to have been discarded. It is necessary, however, to examine the fæces in every case of N.M.A. in this country as associated parasitic infestation may be a complication. Infestation with A. lumbricoides and E. histolytica are not uncommon, but the most important offender is the ankylostome[7,38,39,61,102,105,122,156,159,182,206]. Associated ankylostomiasis is evident in many reports from endemic regions; 21 out of 24 cases of N.M.A. reported by Taylor and Manchandra[182] from the Punjab were complicated by ankylostome infection. The presence of the parasite in a N.M.A. patient does not usually interfere in anyway with the response to specific treatment[38,39], though, at times, it may bring out a change in the blood picture by producing hypochromia (low M.C.H.C.) and eosinophilia. In such cases in addition to the eradication of such infection, iron may have to be administered as a supplement to liver therapy.

THE URINE

Some albuminuria is always present especially in severe cases [7,33,54,102,105,122,182]. More interest centres round the presence of urobilinogen in the urine. Wills[210] noted excess of urobilinogen or urobilin in a single case out of 36. Mudaliar and Narsinha Rao[130] investigated possible increased excretion in 10 cases with negative results. Napier[131,137], in 9 out of 11 cases, found a definite increased excretion, but Chaudhary and Manglik[28] in mere 6 of their 27 cases. Napier[136,137], and Fairley *et al.*[64] found that urobilinuria was constant in the hæmolytic group of N.M.A. but usually absent in the non-hæmolytic group. Same was the experience of Trowell[185]. Kothari and Bhende[105] estimated the urine uribilinogen in a series of 39 cases. Irrespective of hyperbilirubinæmia (as judged by the Van den Bergh reaction), the values fell within the normal limits. Balfour[7] cultured the urine of her patients; various organisms were grown but their ætiological significance would seem to be nil. Fairley *et al.*[64] found that in their series pyelitis was not a common complication.

BIOCHEMICAL FINDINGS

An important investigation in the altered biochemistry in N.M.A. is the determination of the serum—bilirubin value. Wills and Mehta[215] in their first series found that the Van den Bergh reaction was completely negative in uncomplicated cases; they opined that an indirect positive reaction should suggest the presence of malaria or syphilis. The later experience of Wills and her co-workers [212,214] was the same. Similar low or normal values for the serum bilirubin, as judged by the Van den Bergh reaction or the icteric index have been reported by other workers[63,105,136,180,185,187,193], for the majority of the cases. On the other hand, in some series [28,64,72,146,182] the serum bilirubin values are reported to be almost constantly high. Actual estimation of the serum bilirubin was done by Wills[210] in a series of 50 cases; the mean value was found to be

0.33 mgm per cent. Fairley *et al.*[64] found the serum bilirubin constantly raised—the hæmobilirubin level in their series varied from 0.7 to 4.2 mgms. per 100 ml., the average in 37 cases being 2.0 mgms. In Trowell's[187] 8 out of 26 cases the average value was 1.5 mgms. per 100 ml. Upadhyay[193] observed low figures, less than 1 mgm. per 100 ml., in most of his cases. In Callender's[18] series, in those investigated, none showed a higher value than 0.8 mg. per 100 ml. It would appear that cases of N.M.A. fall into two groups on the basis of the serum bilirubin values: the non-hæmolytic group generally showing a normal bilirubin content and the hæmolytic group showing hyperbilirubinæmia. Napier[136] explained that in uncomplicated (non-hæmolytic) N.M.A. there was less anisocytosis and poikilocytosis with few defective red cells to attract the attention of the normal reticuloendothelial system and consequently there was less hæmolysis and low bilirubin content in blood; on the other hand, in the hæmolytic variant, the reticuloendothelium was hypertrophied and abnormal because of previous chronic malaria, with the result that the normal and slightly abnormal red cells were avidly phagocytosed by its cells. Fairley *et al.*[64] agreed with this view as also Wills [210] later on . In the hæmolytic group the hyperbilirubinæmia is associated with reticulocytosis and splenomegaly. The relationship between the three is not always constant. Splenomegaly may not be associated with hyperbilirubinæmia; nor do hyperbilirubinæmia and a high reticulocyte count always go together. Since splenomegaly with hyperbilirubinæmia may not necessarily mean that a hæmolytic process is present the diagnosis of the hæmolytic type of N.M.A. should always be confirmed by demonstration of a raised reticulocyte count. In addisonian pernicious anæmia hyperbilirubinæmia is constant but the reticulocyte count is low. Since malaria is endemic in countries where N.M.A. is common, the original contention of Wills and Mehta[215] that hyperbilirubinæmia is a point against the diagnosis of N.M.A., or in favour of a diagnosis of addisonian pernicious anæmia is no more tenable, at least, in its original form.

Chatterjee[25] investigating the so-called pernicious anæmia of pregnancy in India, found very low plasma cholesterol values in his patients; the values in other types of anæmia associated with pregnancy were lower than normal but the very low figures of the former were never encountered. Nayer[148] found that the plasma cholesterol of normal pregnant females varied from 112 to 247 mgms. per cent. and in the non-pregnant females the range was 100 to 152 mgms. In 19 pregnant females suffering from macrocytic anæmia the cholesterol level fluctuated from 20 to 126 mgms. per 100 ml. Infections —bacterial, protozoal or helminthic—lowered the values still further. The lowering of the plasma cholesterol was not parallel with the reduction either in the red cells or the haemoglobin. In her opinion, disturbance of the reticulo-endothelial system in anæmia was responsible for the low readings. According to her, cholesterol administration cannot replace hepatotherapy (as claimed by Chatterjee[25]) in this anæmia, but it can be used as an adjunct to liver therapy with good results. However, the data supplied in the paper cannot be taken to have proved that such combined therapy is better than specific therapy alone, either in improving the hæmatologic response, or in reducing the mortality in this anæmia, as claimed by the author. Kothari and Bhende[105] studying the plasma cholesterol in a series of 45 cases of N.M.A. in pregnant females were unable to confirm the very low values obtained by Chatterjee[25] and Nayer[148]; though in many cases the readings fell much below the normal range, the lowest value recorded being 80 mgms per 100 ml. No figures are available for the plasma cholesterol value in the males. The plasma proteins are lowered in N.M.A. [38, 39, 105, 168, 171, 180, 186, 193] No figures for serum iron are available for cases studied in this country. Callender [18] reported that in her cases the serum or plasma iron level was high and it fell to normal with the onset of reticulocytosis. Wills and Mehta[215] found that in severe cases there was a slight increase in the blood non-protein nitrogen. Fairley *et al.*[64] estimated the blood urea in 13 patients; the values varied from 13 to 139 mgms per 100 ml. They commented that the raised urea content was the result of increased blood destruction rather than retention and that the renal function was unimpaired. Kothari and Bhende[105] found that in all their cases the values for the blood non-protein nitrogen were within the normal limits. Wills and Mehta [215] were so struck with the low values for serum calcium and serum phosphorus in their patients that they attributed them to a condition of latent osteomalacia due to deficiency of vitamin D in their patients' diet. Mudaliar and Menon[130] similarly noted low values for these constituents. The typical flat curves of sprue, after oral administration of glucose, are not encountered in N.M.A.[64, 94, 210].

It may be summarised that in view of the variable blood picture the valuable aid derived from other laboratory procedures should be utilized in every case. Of these latter, examination of the marrow is the most important. Presence of true megaloblasts is diagnostic and decisive[18, 105]; the basophilic form is commonly found and Ehrlich's hæmoglobinised megaloblast is rare. Presence of free hydrochloric acid in the gastric juice can be demonstrated in the majority of the cases but a histamine-fast achlorhydria does not rule out a diagnosis of N.M.A. (in this country). The faeces should always be scrutinised for any complicating parasitic infestation. If the other findings are compatible with the diagnosis of N.M.A. urobilinuria and bilirubinæmia indicate that one may be dealing with the hæmolytic variant and confirmation of this may be sought for by demonstrating a high reticulocyte level. Hypoproteinæmia and a low cholesterol plasma level are common but by themselves not diagnostic.

THE MORBID ANATOMY POST MORTEM FINDINGS

Few workers have been fortunate enough to study cases of N.M.A. in the autopsy room, and with advances in therapeutics and social medicine the opportunities to study such material are likely to be fewer still. The internal viscera show the general changes of severe anaemia. Wills[210] observed that in non-hæmolytic N.M.A. all the organs—especially the heart and the liver—were reduced in size and weight, a finding which Fairley[60] thought was diagnostic; in contrast, in hæmolytic N.M.A., the body was well nourished and the organs showed an increase in their weights. The spleen is enlarged and gives a positive prussian-blue reaction[7,18,64,78a,185]. Histologically, Balfour[7] found the pulp cords almost extinct and the lymphoid tissue atrophic. Mitra[122], Gupta[78a], Fairly *et al.*[64], Trowell[185], Patel and Bhende[156] could confirm the atrophy of the lymphoid tissue but found that the reticulo-endothelial tissue of the pulp hypertrophic. Extramedullary foci of hæmopoiesis in the sinusoids have been described[788a,131,203], and Callender[18] in her material could identify megaloblasts among such cell islets. In view of the relationship of malaria to the hæmolytic type of N.M.A., it is interesting to note that Fairley *et al.*[64] could detect malarial pigment in the reticular cells of the spleen. The other findings described in the organ are an occasional siderotic nodule in the larger blood vessels, trabecular fibrosis, increase in the reticulum, and, areas of perisplenitis on the surface[64]. The liver may be enlarged[7,18,78a,122,155,185], Fatty change is common[18,64,78a,155] and the prussian blue reaction is usually positive[7,18,64,78a,122,185]. Trowell[185] has pointed out that hæmosiderosis both in the liver and the spleen may be absent in cases of N.M.A. showing coexistent iron deficiency. Myeloid foci in the liver sinusoids have been described[18,78a,122]. The Kupffer cells may be hypertrophic and show in their cytoplasm granules of hæmosiderin and malarial pigment[64]. Hæmosiderin may be present in the parenchymatous cells, mostly at the periphery of the liver lobule[64]. Hæmosiderosis, per se, is not evidence of increased hæmolysis. Mitra[122] found fatty degeneration with extravasation of blood in the centre of the liver lobules and ascribed this to toxæmia(in pregnant females). The kidneys may be enlarged. The tubular epithelium may show granular, fatty or hyaline degeneration and may contain granules of hæmosiderin[18]. The heart showed a typical thrush-breast appearance in 2 of Callender's[18] 3 cases. The adrenals may show hæmosiderosis[78a]. The bone marrow has not been adequately studied at the autopsy ; some observers have described it as hyperplastic ;[7,18,64,78a,122,185]; others call it aplastic in patches or as a whole[7,182,210]. In Callender's[18] 3 cases the marrow was hyperplastic (absorption of the bony trabeculae was present) in all and contained clumps of primitive cells. Mitosis was frequent in such cells. Erythrophagocytosis was detected in all and so was the presence of hæmosiderin in the endothelial cells of the sinusoids and in the macrophages. In those cases where the marrow has been descibed as aplastic mostly the tibia alone was examined. In one instance where the sternum was examined only naked eye observations were recorded[182]. From the sternal puncture material obtained during life it would appear that in the majority of the cases the marrow is hyperplastic and the discrepancies noted may be put down to inadequate study. It is interesting to find that, according to Wills and Stewart[219], the changes in the marrow of the monkeys, in which they claimed to have reproduced N.M.A. by dietetic means, were similar to those seen in the human cases. In view of the pointed difference in the pathogenesis of addisonian pernicious anæmia and N.M.A., special interest centres round the appearance of the gastric mucosa in N.M.A. Only 2 reports are available in the literature up do date. In Callender's[18] single case of pernicious anæmia of pregnancy, the gastric mucosa showed no evidence of any inflammatory change, but, the glands were reduced in size and appeared less complex in formation than normally. Patel and Bhende[155] studied the gastric mucosa in a single proven case of N.M.A. in a male, at a partial autopsy performed half an hour after death. The stomach was normal in size and naked eye there was no atrophy of the wall. Sections were studied from the cardiac fundic and the pyloric regions. Histologically, there were changes of chronic gastritis but no atrophy in any of the coats. The glands in the mucosa were less dense than normally, but there was no distortion of the normal architecture. The lamina propria showed accumulations of lymphocytes and plasma cells. The submucosa was widened and showed small collections of lymphocytes and plasma cells. Though the authors refrain from drawing any conclusions from the study of a single case they point out that, in contrast to addisonian pernicious anæmia where the gastric mucosa shows a non-inflammatory atrophy (Magnus and Ungley[113]) which could be held responsible for the loss of the intrinsic factor, in N.M.A. the loss of the extrinsic factor does not produce the same change. In the experimental N.M.A. of the monkey the gastric mucosa was found to be normal[210]. In contrast to these differences in the structural abnormalities of the stomach in the two diseases, the functional abnormalities in the gastro-intestinal tract in addisonian pernicious anæmia and N.M.A. appear to be very similar, since the gastro-intestinal symptoms are relieved uniformly in both the diseases by liver extracts or folic acid. No nervous lesions have been described in N.M.A. in the autopsy material.

REMISSIONS AND RELAPSES

Prior to the introduction of the liver therapy, spontaneous remissions, though incomplete, featured commonly in the natural history of addisonian pernicious anæmia[202,224]. Similary, spontaneous remissions after delievery, are considered a characteristic feature of the so-called pernicious anæmia of pregnancy[18,64,138,202,224]. Wills [203] observed "once the delivery is over and the first two days are safely passed, the majority of the patients go into natural remissions". A critical examination of the records, however, gives no information as to whether such remissions are complete. In both addisonian pernicious anæmia and the so-called pernicious anæmia of pregnancy, the remissions have been explained as due to resumption of the secretion of the intrinsic factor by the gastric mucosa[175,176]. In contrast such spontaneous remissions have never been observed in N.M.A. in the males or the non-pregnant females. Wills, Clutterbuck and Evans[212] remark that in a series of 200 cases a natural remission, except after delivery, has never been seen by them. Again in contrast to addisonian pernicious anæmia, in N.M.A., once the blood has been restored to normal level by specific therapy the patient can be successfully rehabilitated by prescribing a good diet alone and no relapse need be feared. Recurrence of the anæmia, however, is not unknown in subsequent pregnancies[159].

(To be continued.)

ACUTE POST-INFECTIOUS NEPHRITIS IN CHILDREN

G. Coelho *

Ellis[7] divided nephritis into two types; Type I with an acute onset and Type II with an insidious onset. Of his 173 cases of Type I, 60 per cent fell within the first two decades and 46 of them were below ten years of age. Hence acute nephritis is more often a disease of children. In my series of 38 cases seen in two years none were below 2 years, 12 were between 2 and 5 years, 14 were between 6 and 10 years and 12 were between 11 and 13 years.

ETIOLOGY

The etiology of this condition is still not settled. Many cases follow an acute infection, especially of the upper respiratory tract, and so this has been held responsible. As actual bacterial invasion of the kidneys has not been proved it is said that the damage is caused by the bacterial toxins that are excreted through the kidneys. Farr[8] produced nephritis in rats by injecting nephrotoxic sera, though in the early stages the histological picture was that of nephrosis. Still there is a period between the acute infection and the renal manifestations and this has prompted the suggestion that nephritis is an allergic phenomenon. Press, Longcope and O'Brien[11] demonstrated that a large number of cases of acute nephritis gave a marked allergic reaction to filtrates from cultures of streptococci injected intradermally.

Histologic studies of the kidneys in the acute stage are not many as few reach autopsy. Aldrich[1] finds a complete lack of uniformity in the post-mortem findings. One of his cases showed hyalinisation of the glomeruli even as early as three weeks, another extensive tubular degeneration and hyperæmia in the medullary portions, while in a third the changes in the kidney were negligible. In summarising he writes—"there is great variation in the extent of renal involvement, the glomeruli show changes which may be generalised and of a highly destructive nature, or localised in a few areas and insignificant in degree. The

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tubular changes are not severe as a rule." Seven of Ellis'[7] patients died in the acute stage; their kidney showed severe glomerular and tubular changes.

SIGNS AND SYMPTOMS

Most of the children are brought with one of the following complaints, in the order of frequency :—1. Scanty urine, 2. Puffiness round the eyes on rising in the morning and 3. Smoky urine.

In addition there may be fever, headache, vomiting, drowsiness, convulsions and loss of vision.

1. *Oedema*:

This may be limited to the face, round the eyes and seen only in the morning on rising. This will be in the mildest of cases. Generally it is more extensive—of the lower extremities and even of the whole body and persists the whole day. Such œdema is hard and does not pit on pressure. Sometimes the swelling is so uniformly spread that its variation can be detected only by weighing the child daily. In my experience ascites and hydrothorax are rare in this condition.

2. *Infection*:

There may be signs of infection in the throat or on the skin. The tonsils and pharynx are congested, the tonsillar glands are enlarged. At the time the child presents himself for examination this infection may have settled down. On the other hand, skin infection is seen more often. Of late, scabies with secondary infection is the commonest infection.

3. *Urine*:

The appearance may be that of frank blood or it may be smoky. In both these states there is oliguria. In milder conditions any definite colour is not noticeable, neither is there marked diminution of the urine. Albumin is always present, beginning from a haze to a pronounced precipitate but an excess is unusual. Red blood cells are seen in abundance, at least 20 per field in the mildest of cases. Casts, granular and cellular, are also always present.

4. *Blood Pressure*:

There is a rise in the blood pressure. A systolic pressure above 115 mg. Hg. in a child 6 years old is significant. The pressure varies between 130 and 160 mm. Hg.; it once reached 250 mm. Hg. in a girl 4 years old. Even with pressures up to 160 mm. Hg. the children move about without any signs of discomfort. The rise in pressure may be sudden.

5. *Encephalopathy*:

A high blood pressure is associated with one or other of the following :—headache, vomiting, a cloudy mind, drowsiness, coma, convulsions, loss of vision. These may appear suddenly with the sudden rise of pressure.

The rise in blood pressure and the cerebral symptoms are due to œdema of the brain. Volhard and Farr[12] were not certain as to which was primary and which secondary. According to Marriott[9] a toxin causes capillary constriction and the uræmia. But Boas[3] found that the capillary pressure was normal in a number of cases of acute glomerular nephritis. Experimenting with dogs Cushing[6] found that the arterial pressure rose as the intracranial pressure increased. Blackfan[2] observed that the cerebral symptoms disappeared and the blood pressure fell while the œdema decreased. In my experience the blood pressure falls first, followed by an improvement in the cerebral symptoms, with or without diminution of the œdema. Blackfan[2] writes—"It is not to be denied that alterations in the capillaries may be the primary cause of the œdema." He thinks that the cerebral symptoms may be explained on the basis of cerebral œdema and increased intracranial tension, and supports his idea on the action of hypertonic saline and one per cent. solution of magnesium sulphate. Ellis found neither spasm of the retinal blood vessels nor increased intracranial pressure in his cases of hypertensive encephalopathy.

6. *Fever:*

This may be present. As the nephritis follows some days after the primary infection, in the majority of cases there is no fever.

7. *Blood Chemistry:*

There is an increase in the blood urea which ranges between 30 and 60 mg. per 100 c.c. of blood in the majority of cases. Neither the œdema nor the oliguria nor the blood pressure run parallel with the rise of blood urea. The blood cholesterol and the plasma proteins are unaffected. In the early stages the red blood cells and haemoglobin are normal; if the haematuria persists for some days there is fall both in the cells and in the haemoglobin.

8. *Myocarditis:*

Toxic myocarditis is one of the serious complications. Enlargement of the heart, tachycardia and alteration of the heart sounds are the first signs. Later there is enlargement of the liver.

DIAGNOSIS.

Haematuria, oedema and hypertension form the diagnostic triad. The following have to be considered in practice:—

1. Scanty urine. The child is brought because he or she passes very little urine. It is found that the fluid intake is restricted and the urine does not contain any red blood cells or casts.

2. Pyelitis. In this, though there may be a trace of albumin, and a few red blood cells, the pus cells are in excess of the red cells. There are no casts, nor is there hypertension.

3. Febrile albuminuria. In many a febrile condition, a trace of albumin in the urine is reported. This does not warrant a diagnosis of acute nephritis. Sometimes there may be a few red blood cells, and occasional casts. Then one has to wait and watch. As there is neither oliguria nor oedema nor hypertension nor a rise in blood urea, I have never submitted them to the treatment for nephritis.

4. Haematuria and oliguria may follow the administration of sulfa drugs, particularly when sufficient fluid is not taken. In my experience this has been very rare. In the course of ten years use of sulfa drugs, the number of cases with haematuria would not exceed a dozen. This haematuria may occur early or a few days later. Microscopically the field is packed with red cells, but there are no casts. The blood pressure is normal.

5. Stone in the kidney, tubercular infection of the kidney may cause sudden haematuria. But oedema and hypertension are absent.

6. Puffiness of the face. Some children are brought with this complaint with the fear that the child may have nephritis. This may be due to anaemia, hypoproteinaemia, and sometimes infection of the sinuses. Nephritis is an unusual finding in this group.

7. Diagnosis from nephrosis and chronic nephritis. Red blood cells and hypertension are foreign to nephrosis. But an acute condition may be super-imposed on a nephrotic kidney or a chronic nephritis. Here history and a follow up of the patient will be a guide.

PROGNOSIS :

Acute post-infectious nephritis has the best prognosis of nephritic conditions. With rest and adequate treat ment, the blood pressure falls in 3 or 4 days, the diuresis sets in about that time, the œdema begins to decrease at the same time and is very little in a fortnight's time. The changes in the urine are more gradual. The red blood cells and casts disappear very slowly, the red cells may remain as long as six months.

A rapid rise in blood pressure, vomiting and head-ach e are danger signals. Myocarditis has a bad prognosis.

TREATMENT.

1. *Rest in bed :*

All clinicians lay great stress on this and consider it as the most important part of the treatment. But my difficulty has been in enforcing it. Very few children remain in bed. Even with marked oliguria and a blood pressure approaching 150 mm. they move about unconcerned.

2. *Magnesium Sulphate :*

This is the sheet anchor on in the treatment of Encephalopathy and Hypertension. It may be given orally, intramuscularly, intravenously. The oral route is used in all cases when the child is conscious and the blood pressure is below 150 mm. Hg. A well-sweetened, saturated solution is administered as follows : up to 5 years—2 drachms four hourly, 5 to 10 years—4 drachms four hourly and above 10 years 6 drachms four hourly. When the the blood pressure is over 150 and fast approaching 200, when there are signs of encephalopathy, magnesium sulphate should be given intravenously, as it relieves the symptoms dramatically. Either one per cent. or four per cent. solution in 5 per cent. solution of glucose is used. Of the former 5 c.c. and of the latter 1.25 c.c. per pound weight is used. The injection, particularly the four per cent. solution must be given slowly, the rate being not more than 2 c.c. per minute. When it is difficult to get a vein a 25 per cent solution should be administered intramuscularly. The intravenous and intramuscular injection must be repeated every 8 hours till the patient regains consciousness and the blood pressure has fallen below 150 mm. Hg.

Two explanations have been offered for the action of magnesium sulphate. One, that it has a sedative action, releasing the capillary spasm and second that it brings about a change in the osmotic relationship between blood and tissues of the brain. Blackfan[2] thinks the dose of magnesium sulphate is too small for its sedative action and the beneficial effect is due to an alteration in the osmotic relationship. He also writes of the cathartic action of magnesium sulphate, but in our experience we have noticed no such action when administered in the dosage mentioned above. This favours the sedative action of magnesium sulphate.

For the headache and convulsions I have found the quickly-acting sedative seconal-sodium (Lilly) quite satisfactory. But any sedative could be used. Electric cradles and cupping have no place in the treatment of this condition. Neither is venesection nor a lumbar-puncture indicated.

3. *Control of Infection :*

It is unusual to find a state of acute infection of the throat with this nephritis. When there have been such signs I have used sulfa drugs without hesitation. I started with prontosil then moved on to sulfapyridine and now to sulfadiazine. There have been no bad effects. With the introduction of anti-biotics, penicillin, orally or parenterally, is advised and this is administered freely without the mental reservation of the sulfa drugs. There is no indication for its use unless there are signs of infection—temperature and a leucocytosis.

The treatment of scabies has been made easier by the introduction of emulsions of Benzyl Benzoate. For the secondary infection a sulphathiazole ointment or a triple dye application is useful.

4. *Fluids:*

For some time there has been a controversy regarding fluids and diet. Fluids have been restricted from a long time and are being restricted even now. Ellis[7] is in favour of restricting the fluid intake to one pint of fruit juice for an adult and so also, Christian[5]. From 1933 onward I have not restricted fluids as I found that inspite of restrictions on paper children helped themselves freely and were none the worse for it. In 1936 Neuburgh[10] drew attention to the harm done by fluid restriction and brought experimental evidence to demonstrate that the kidneys of oedematous subjects were able to secrete a very large amount of urine containing a normal amount of solids as soon as they were permitted to drink a sufficient amount of water. After his attention was drawn to it by Brennemann, Aldrich has not denied water to any of his patients and "no patient so treated has died of acute post-infectious haemorrhagic nephritis." Irrespective of oedema, every child should be encouraged to drink at least 2½ ounces of fluid per pound weight per day. This fluid may be in the form of plain water, fruit juices, aerated water, cereal water, vegetable soups.

5. *Diet:*

"Ideas on the management of a developed nephritis of any type have been considerably modified in recent years. We recognise that the disease is by no means limited to the kidney" (Christian). I have been adding more articles to the diet of these children. The first additions have been fruits—bananas, papayas, oranges, sweet-limes, chikoo, and apples according to their availability. Then rice and bread and butter and milk and vegetables. The condition of the patient and the progress has not been affected adversely with the additions of these items of solid food. If protein could be given as milk, why can it not be given in other forms? So recently I have been allowing meat and eggs; the cases have been few, but their behaviour has been about the same as those with water only. Boyd[4] writes "often empirical therapy has been based on a misinterpretation of physical or laboratory signs. For example, when abnormality of the kidney or of the urinary constituents has been apparent, it has been rationalised that the kidney should be put at rest; that substances requiring elimination through the kidney should be withheld from the diet. This has served as the rationale for the limitation of protein foods, salt and water in the treatment of albuminuria, oedema, haematuria or manifest renal disease of any type." Aldrich reported that those with restricted diet did not do any better than those who were allowed protein. Hence I think that our attitude towards the diet in nephritis needs a reorientation.

SUMMARY.

1. Acute post-infectious nephritis is more common in children.
2. Haematuria, hypertension and oedema form the diagnostic triad
3. A rising blood pressure, headache and vomiting are danger signals.
4. Of all types of nephritis, this has the best prognosis.
5. Rest in bed, liberal intake of fluids and magnesium sulphate is the treatment.
6. Solid food in the form of fruits, rice, vegetables, bread and butter and even meat has not acted deleteriously in this condition.

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CURRENT MEDICAL LITERATURE

SURGERY

THE USE OF BRILLIANT GREEN IN THE TREATMENT OF CHRONIC ULCERS OF THE SKIN. FEINBERG, A. W., New Eng. Jour. Med. 239 : 613-615, 1948.

Experiences with the dye brilliant green in a series of cases of chronic skin ulcers are described. A 2 per cent. solution in distilled water was used. After thorough cleansing of the ulcer with hydrogen peroxide and alcohol, the dye was painted daily until healing was progressing well—generally about 7 days. It was then applied every other day until healing was complete. The ulcer was covered with a dry sterile dressing after each treatment. Rest was advised and the affected extremity was kept elevated during sleep. The results in 20 cases were excellent and justify further extentended trial of brilliant green in chronic ulcers.

E. J. BORGES.

PULMONARY VALVULECTOMY FOR RELIEF OF CONGENITAL PULMONARY STENOSIS. BROCK, R. C. Brit. Med. Jour. 1 : 1121-1126, 1948.

Although the great Bilroth in 1883 described operations on the heart as a surgical frivolity much advance has taken place in cardio-vascular surgery in recent times. The author describes 3 consecutive successful cases of intracardiac operations for stenosis of the pulmonary valves done in February-March 1948. The first operation for relieving pulmonary stenosis was done by Blalock of Baltimore in 1944 and since then the operation usually done for this condition is the Blalock-Taussig operation which consists of by-passing the stenosed area by anastomosing a systemic artery, such as the subclavian, to the right or left pulmonary artery. In this way additional blood is supplied to the lungs and the immediate results have been very good. What the late results will be is difficult to predict but two possible draw backs occur to the author : First, the fistulous communication may not grow *pari passu* with the child, and secondly one actually creates a condition of artificial ductus arteriosus.

For the above two reasons the author devised the vulvulectomy technique. He found the approach through the pulmonary artery unsatisfactory. His 3 successful cases were done with the help of a specially constructed cardioscope and valvulotome passed through the right ventricle and through the stenosed valve into the pulmonary artery. A dilating forceps inserted was opened fully to dilate the valves. Previously inserted two rows of 3 interlocking sutures of linen thread prevented hæmorrhage.

The operations were done on 3 girls aged 18, 11 and 23 years. Postoperatively the first girl had an arterial embolism in the legs, and the third girl had a left hemiplegia due to a similar cause. In all the 3 a diagnosis before operation of Fallot's tetralogy had been made.

E. J. BORGES.

INFLAMMATORY CARCINOMA OF THE BREAST. A. C. MEYER, M. B. DOCKERTY, S. W. HARRINGTON, S.G.O. 87 : 417-424, 1948.

The authors state that it's a matter of common knowledge to clinicians to find malignant lesions simulating an inflammatory process. These lesions have been described under many apt names. During 1933 to 1945 the Mayo Clinic received 7,000 cases of breast malignancy of these 74 cases showed redness and œdema of the skin and an analysis of these cases is given in detail.

The incidence of the so-called inflammatory carcinoma comes to 1 per cent. of all breast malignancies and the average age was 52.6 years. Peculiarly the left breast was involved twice as often as the right. Ten cases or 13.5 per cent. eventually had bilateral carcinoma at varying periods, and the duration of symptoms averaged 7 months. 14 cases (18.9 per cent.) were diagnosed as inflammatory disease and treated as such. The affected breast was found symmetrically enlarged in 38 cases although in most carcinomas this is uncommon. 73 per cent. had redness of the skin and 78 per cent. had edema which was not due to malignant infiltration of the skin and was a true inflammation. 53 per cent had pain at some time during the course of their disease while 26 per cent. had it as the first symptom.

On pathological examination the overlying skin was thickened and edematous while the tumour was found to be diffuse and extensive in the breast tissue as the malignant cells spread quickly along the lymphatic vessels. The sub-epidermal lymphatics were involved in 80 per cent. of the cases while cancer cells were absent from the epidermal layer of the skin. In no instance was there evidence of acute inflammation or suppuration. 88 per cent. of the lesions were of Broder's Grade 4, all were adenocarcinomas and 5 were producing mucus. Axillary node metastases was present in 100 per cent. The main characteristic of this growth was the extensive lymphatic dissemination especially towards the skin.

In 61 of the 74 cases a radical mastectomy was performed, and in 2 a simple palliative mastectomy. All but 1 case had post-operative radiation.

The authors think that the redness and edema are due to stasis and tends to disappear when the patient lies down. The phenomena is one of passive hyperemia.

The prognosis is very poor in these cases and hence some writers have suggested palliative irradiation as the treatment of choice. Only 3 patients lived for more than 5 years and 1 was alive 9 years after operation. The common sites of metastases were thorax, bone, opposite breast and frequent metastases to the skin.

R. J. MANEKSHA.

THE PROSTATIC PATIENT : PREOPERATIVE APPRAISAL AND CARE. WILLIAM BAURYS.
The Surgical Clinics of North America. 28 : 1351-1359, 1948.

The process of tissue atrophy, the usual change accompanying senescence, is reversed in the prostate and why nature causes hypertrophy of this gland is a mystery.

About 10 per cent. of hypertrophies in men past 60 require operative correction. The ageng patient with symptoms of frequency and nocturia is not always a prostatic patient and may deceive the overzealous operator, while an impressionistic patient may also develop mental fixation of having an enlarged prostate.

A large gland is not always an obstructive gland—an enlargement requiring operation is not determined by palpation alone.

Alcoholic excesses are known to transform a threshold prostate into an obstructive one—the author states that alcohol is one of the few substances excreted by this gland. The management is to temporize during the attack with frequent follow ups.

Carcinomatous Prostate—Not every patient with a carcinoma needs an immediate operation especially if asymptomatic. For obstruction, a transurethral resection and for metastases-orchidectomy and stilbestrol are used.

Preoperative Studies—The candidate for surgery of bladder neck obstruction presents several problems—main being geriatric, cardiovascular and surgical. The particular specialist is called in for consultation the cardiologist as a routine. The author denies operation to moribund and insane patients only an indwelling catheter is resorted to. The patients are permitted and encouraged to be ambulatory.

An indwelling catheter is preferred to the suprapubic cystostomy. A Wasserman test is done as a routine—in such cases caution is necessary to distinguish from tabetic type of bladder with atonic distension. Blood transfusion is ordered when the R.B.C. is below 4 million and hæmoglobin below 70 per cent. A high sedimentation rate is suggestive of malignancy with secondaries. Blood urea nitrogen is the most important test—operation is done when the level has reached a stable point although blood urea over 100 mgm. is no bar to operation. An acid phosphatase considerably above normal is suggestive of malignancy although a low level may be present also specially when secondaries are absent. The most reliable test for diagnosing malignancy is the examining finger. For intravenous urograms Neo-Iopax is used—the injection is stopped after giving the first 2 cc to see if any symptoms appear. The cystogram shows diverticula and the contour of the bladder with the size of the prostate.

A mixture of sulphadiazine and sulphamerazine is given as a routine either as curative for pyuria or as a prophylactic measure—Syrup Ammonium Mandelate 2 drams four times a day gives spectacular results when B coli don't respond to the sulphonilamides. Urosepsis is no bar to operation except with high febrile reactions. Streptomycin has proved a rather poor urinary antiseptic.

R. J. Maneksha.

PEDIATRICS

Infantile Gastroenteritis treated with Streptomycin by Mouth. Ursula James, I. R. H. Kramer and P. Armitage. The Lancet 2 : 555-561, 1948.

The authors treated thirty cases : four of these were the most severe ones in an outbreak of epidemic diarrhœa of the newly-born, four were selected during an epidemic of gastro-enteritis in a residential nursery and 22 were from a Children's Unit. All the cases when submitted to streptomycin were severely ill and 19 out of the 22 cases in the Children's Unit were those who had not responded to routine treatment. P. *vulgaris* was isolated from the stools in 19 of these thirty cases, P. *morgan* was found in one, and the rest were negative.

Streptomycin was given by mouth so diluted that the fraction of the daily dose to be given at each feed was contained in 1 ml. Barring 4 cases, 2 of whom received 2 g. in 4 days and 2. 1g in 4 days, the rest received 2 g. in 7 days : 0.5g. in the first twenty-four hours, and 0.25 g. in each subsequent 24 hours for a further of 6 days. 28 of the 30 cases responded satisfactorily. The gain in weight was spectacular. This was demonstrated by a controlled observation to be due not to any specific action of streptomycin as healthy children did not gain in weight, but to an improvement in the general condition : the improvement in the stools followed the general condition ; their frequency persisted for three or four days, but the consistency improved gradually. Bacteriologically there was a rapid fall in the number of organisms in the stools. P.

vulgaris disappeared from the stool in as short a time as 4 hours. No growth could be obtained from the stools for a few hours to several days after which the normal flora gradually returned. Vomiting ceased early, the appetite improved, the period of starvation was reduced, milk feeds were well tolerated, the daily caloric intake being rapidly increased at the rate of 100 calories per day; and the stay in hospital was very short. Should there be a parenteral infection it should be treated. Gastro-enteritis of virus origin will not respond to streptomycin by mouth.

G. COELHO.

STREPTOMYCIN IN THE TREATMENT OF PERTUSSIS. H. LEICHINGER AND A. SCHUTEZ. J. Pediatrics 33: 552-555, 1948.

A small series of children suffering from whooping cough, aged 6 weeks to 5 years, were divided into groups, and were observed in the wards for 3 days; a note being made regarding the number and duration of the paroxysms. After that they were treated with Streptomycin for seven days. Group I received the drug by the aerosol route and Group II intramuscularly. For the aerosol treatment one gram of streptomycin was dissolved in 8 c.c. of normal saline and 1 c.c. given every three hours round the clock with a Nebulizer. The second group received one gram of streptomycin daily in 8 divided doses. The results after seven days were compared with a third control group who received only symptomatic treatment. Trained observers attested to the efficacy of the streptomycin treatment especially by the aerosol route as shown by the decrease in the number of paroxysms, the marked decrease in complications and the clinical impression.

G. COELHO.

CONVOCATION ADDRESS BY THE HON. RAJKUMARI AMRIT KAUR AT THE COLLEGE OF PHYSICIANS AND SURGEONS, BOMBAY, ON THE 4th JANUARY 1949.

I consider it a privilege to have the honour of delivering the Convocation Address at the College of Physicians and Surgeons at Bombay and am grateful to the authorities for having given me the opportunity of associating myself with your function today. I confess that the invitation came to me as a surprise. The distinguished persons who have addressed you in previous years were men of outstanding merit in the medical world who, by reason of personal experience were in a position to give wholesome advice to the students attending the Convocation as well as to speak with technical authority on the main health problems of the country. I presume that I have been invited to share this honour mainly because I am privileged to be the first servant of health administration in the Government of India and also because of my long connection with social work in many fields. In recent times, the scope and content of medical service have been rightly recognised as being something far more than the mere ministration of medical care, and medical men themselves have been foremost in insisting that in interpreting health and disease man must be considered in relation to the totality of his physical and social environment. Such a conception naturally emphasises the importance of the part that social service in its manifold forms can play in the development of a national health programme. Hence it is primarily as a social servant that I shall share my thoughts with you today for I am of opinion that, since the great profession to which you have the honour to belong is meant by God and nature for healing the minds and bodies of sick and suffering humanity you are, first and last, servants of society in the highest sense of the term.

On the last occasion the Convocation Address was delivered by my distinguished colleague and friend, Dr. Jivraj Mehta and he, with his wealth of experience in the two fields of medical education and health administration, drew a comprehensive picture of what the country needs for the development of our national health programme. I am in full agreement with all that he said and it will be unnecessary for me to attempt to supplement his observations by any special remarks on many of the aspects on which he touched and which must be fresh in the minds of those of you who heard him. I shall turn the greater part of my attention to certain spheres of health activity in which, as a layman, I feel more at home.

I am of opinion that the doctor of the future, if he is to fulfil his mission of promoting the mental and physical health of our people to the highest possible level, should be a person of culture with many interests and one possessing wide sympathies. He should equip himself not only for the giving of medical relief to the people but also for helping them to prevent disease by knowing how to adopt and maintain that hygienic mode of life which alone will secure for them a full measure of capacity for productive work and for the enjoyment of life. This broader outlook on the functions of a doctor brings with it the need for a new approach to the promotion of community health service, so that the contractual basis whereby medical aid is now made available to the people in relation to their ability to pay for such services may be replaced by a programme which provides adequate health protection as one of the 'national minima' which the individual citizen has the right to demand and secure. I venture to hope that, in such a comprehensive development of health services, the doctor of the future will find himself relieved from the continual pressure of a fiercely competitive world which today makes it difficult for him either to secure a life of reasonable comfort or give himself any opportunities for cultural development and that he will find his energies liberated for that fuller collaboration with his fellow medical men and other workers in the medico-social field which is so essential for the building up of a national health programme on sound lines. I shall try to explain at some length each of these points of view which I have put forward.

Today the emphasis in the training of a doctor is on the development of his professional capacity. This is as it should be. The community has the right to demand that those who deal with the physical and mental disabilities of the people shall be as competent as possible from the technical point of view. Indeed everyone must view with concern all attempts to lower standards of medical degrees on the plea that we must give some sort of aid and relief to the rural areas. Lowering of standards of education can never be a remedy for any disease. On the contrary they will, in the long run, defeat the very object in view. We must therefore stand for the M.B.B.S. as the minimum registerable degree for practitioners and I sincerely trust that all licentiates will take immediate advantage of the condensed courses now available to them. Modern medical science progresses at a rapid pace and it ill becomes members of the profession not to be up-to-date in every branch of the science. We must therefore have immediate and adequate upgrading of our colleges and I am longing for the day when we can lay the foundation stone of the All-India Medical Institute, a dream that has too long remained a dream. In this connection I am glad to note and hope it may be possible in the near future to carry out the recommendations of the recent conference of Vice-Chancellors and representatives of Medical Faculties of our Universities which was called by my Ministry to suggest ways and means of maintaining a high and uniform standard of post-graduate study all over the country. At the same time technical skill and competence must always be supplemented by the human approach. The doctor often comes in contact with a patient when he is in a state of acute mental distress and on other occasions he may be suffering from a varying degree of mental and physical discomfort. An essential need for promoting recovery is that the doctor should be able to secure and maintain the respect and confidence of his patient. A mere technician, however expert he may be, will not always be able to do this by means of his medical skill alone. Understanding and sympathy, tact and patience are all necessary for winning the confidence of the patient and these qualities need to be cultivated if a man or woman is to become a successful doctor. The idea of social service can and should be fostered as part of the medical training. In addition some acquaintance with the humanities may well be considered as a necessary background of cultural training on which medical education should be built. I see no limit to the possibilities of enduring work for the people if our doctors and other health workers are permitted to secure an adequate background of general culture. The place of medical men and women in the lives of their patients is a unique one. The circumstances in which they meet and minister to their needs should help doctors to obtain an immense hold on their patients and, if the influence so secured is wisely used, the opportunities for directing their loyalties to right causes are innumerable. The world cries out today more than ever before for a re-orientation of our outlook and for a fresh affirmation of our faith in the fundamental values of life. The progress of science has placed so much power in our hands that if, on the one hand, we turn it to destructive purposes we may eliminate man and his civilisation altogether from the face of the earth. On the other hand, if we use it wisely and well, we may control effectively disease, disfigurement and destruction as well as secure the production of all the things that are needed for the promotion of the health and welfare of mankind. The medical man as a biologist and scientist is perhaps in a better position than others to understand and appreciate the fact that the worth and dignity of the individual must be the fundamental basis on which the structure of civilization should be built. Community life can be best developed and maintained on a harmonious adjustment between the needs of the individual and those of the group or nation to which he belongs. This adjustment is possible only if, through education in a wide sense of the term, each man is able to secure a balanced and broad outlook on life and its obligations in relation to himself and others. Much of the hate and distrust that exist, whether between nations or between groups within nations, are due to the fact that an integrated development of human personality has hardly been possible in the past through lack of cultural education on sound lines: It is true that various economic and social factors have largely militated against such cultural development. But even with the removal of economic disabilities the moral and psychological conflicts that exist in the individual are likely to remain, unless he can be re-educated to a sounder conception of fundamental values. The physician of the future should be able to use all the means at his command which modern psychiatry provides, in order that he may participate in a campaign for the improvement of the mental health of our people. In addition as I have already stressed he should possess a wide cultural background himself if he is to be in a position to help effectively in this campaign. I, therefore, hope that some of you, at any rate, will specialise in psychological medicine.

I have already referred to the fact that the emphasis in the past has been more on the treatment of disease than on its prevention. If the physician of the future is to fulfil his mission truly, he will have to concentrate just as much, if not more, on the preventive as on the curative aspect. I envisage that he will, in addition, have to engage himself more and more on the development of measures designed to promote positive health. Medical supervision of work and play, adequate control over the environment, including food and water supplies so as to eliminate factors inimical to health, periodical examination of all the members of the community in order to detect and treat departures from normal health in their early stages as well as health education of the people so as to inculcate hygienic habits of life, these and many other duties of a similar nature will, I have no doubt, become increasingly recognised as part of the functions of a national health service. It is a tragedy that today we have not even in our cities a compulsory medical examination of our school children nor a free meal for them. In such a programme of health endeavour there will hardly be any room for the contractual basis of medical service to the people. The State will have to ensure that each citizen secures such medical care as his condition demands and this may not be dependent on the extent to which he can purchase the required service. If these conditions are to be fulfilled, a socialised health service functioning at the highest level and providing health protection to all the citizens will have to be our objective and in such an organisation there will perhaps be little room for private practice.

I anticipate that the doctor of the future will become a full-time public servant who will be required to devote all his energy to the duties entrusted to him by the State. I realise that the fear is widely held that such a development is likely to kill initiative as well as to blunt the edge of that ambition which now urges the man of ability to exert himself to excel over his co-workers. Surely such a danger should not really exist? In any event the way of meeting it should not be by refusing to move forward towards a socialised health service on the lines indicated but by promoting and establishing other and more socially desirable incentives for advancement than self-interest. Extended facilities for self-expression through study and research, opportunities for rise to positions of responsibility and trust as well as a general re-education of the individual so as to increase his sense of obligation to the community should, I urge, be some of the lines to be followed in stimulating the individual to give of his best to the service of the community. I hope many amongst your number will be drawn to a career of research so essential to scientific progress. This land offers in a special way a wide field for research not only in diseases of varying nature but also in our indigenous drugs and in our ancient systems of medicine which have, for whatever reasons, remained static for centuries.

This is the long term picture of health development as I see it. Today the position is quite different. The rates of morbidity and mortality are very high in the country. Our resources in trained personnel, institutions and funds are all too meagre to meet the requirements of the country. The number of doctors in relation to the population is somewhere in the region of 1 to 6,000 as against 1 to 1,000 in the United Kingdom and 1 to 750 in America; the number of nurses is in the region of 1 to 43,000 of the population as against 1 to 300 in England. The number of midwives is only about 5,000 in India. The Bhore Committee, while estimating the expansion that would be necessary within the period of a quarter of a century for the organisation of adequate health services, pointed out that in the case of doctors the increase would be in the region of four times, in the case of nurses about 100 times and in the case of midwives about 20 times. And what about dentists? I believe I am right in saying that in the whole of India we have barely 1,000 well qualified practitioners of dental science. It will thus be seen that the need of the hour is very much more for a rapid increase in the number of ancillary personnel such as dentists, nurses, midwives, etc. A disheartening feature of the situation is that even the existing number of doctors is not properly utilised for the benefit of the country. About 75 per cent. of them live in urban centres while the population of the rural areas is seven or eight times that of the cities. Every inducement should be given for promoting the flow of doctors, nurses and other health personnel into the rural areas through the provision of better pay for such service as well as the development of amenities in the form of satisfactory housing, places for recreation and educational facilities for children. These conditions must be associated with any schemes of health development for the rural areas put forward by Government in the country.

The present time is scarcely propitious from the point of view of Governments undertaking any large scale expansion of health services. The aftermath of Partition in the shape of the refugee problem, the Kashmir trouble and various other factors have all tended to swallow up the resources of the country leaving very little for constructive work in such fields as those of health and education. Even so, we at the Centre have not been standing still. In order to make some beginning in the matter of providing post-graduate training facilities in the country itself, the Government of India appointed an Upgrading Committee which is expected to report shortly and put forward proposals for developing training in particular subject at different medical colleges and research institutions in the country. The subject of environmental hygiene is of supreme importance to the health of the community. Good food, fresh air, a clean water supply and hygienic houses are really more important than drugs, vaccines and sera for enabling the people to lead healthy lives. A special committee appointed for the purpose has been investigating the problems of environmental hygiene and it is hoped that its recommendations will prove to be of great value to the health authorities of the Central Provincial and State Governments in developing this branch of health administration.

In this short address I have had time to refer only to certain aspects of our health problems. Before I conclude let me, however, draw special attention to one or two matters which I consider to be of great importance. Medicine even more than other professions requires the services of the best men and women who are available. Our teaching and research institutions in particular must be manned by those who, by their ability and training will be able to contribute to their efficient functioning. I therefore stand for the elimination of any narrow sectarian or provincial outlook in making appointments to such institutions. I would even urge that, in this transitional period, we should not hesitate *if necessary* to obtain the services, on short-term contracts, of suitable specialists from abroad until our own people can be trained to take up these responsible posts. Nothing but the promotion of the best interests of the country should be permitted to have any influence on the development of our health services and particularly of those which are concerned with the training of doctors and other health workers and with the running of our research institutions.

Friends, I congratulate all who have secured degrees and wish you well in your careers. You are members of one of the noblest of professions. May you never tarnish its fair name. Service from you is demanded by the masses who have been terribly neglected up till now and cannot even today get their due because of lack of facilities and personnel. It is your duty to see that they are not exploited as they so often are by quackery. They need single-eyed devotion and if your treatment and education of them springs from love you will have their devotion in abundant measure which will be worth far more than returns in silver and gold. I feel that India calls in a special manner to doctors and nurses, men and women of the highest calibre in character and professional skill. It is yours to help your national governments both at the Centre and in the Provinces to usher in a new era in the realm of health. I appeal to you specially on behalf of our young mothers and children. The high incidence of mortality among the mothers of the race and the future generation must be reduced. Malaria and tuberculosis must be combated as also the other epidemics that take such a heavy toll of life. Above all it is for you in your great sphere of service to set a high standard of integrity so that you may help India to rise to her full stature and maintain her erstwhile reputation of laying the greater emphasis on what matter most—namely, the moral and spiritual values of life. May you be given the necessary strength to give of your best and thereby find yourselves in service to humanity is my sincere wish for each one of you. May life be for you a mission, its end not the search after happiness but a quest for knowledge and the fulfilment of duty.

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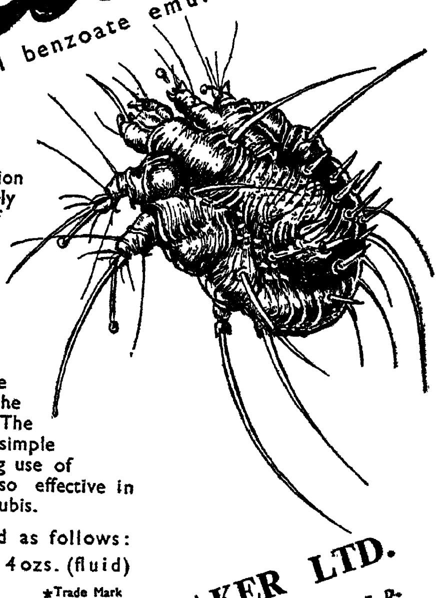

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AMŒBIC LIVER ABSCESS §

W. D. Sulakhe *

INTRODUCTION

The incidence of amoebic dysentery in India is widespread. The natural history of this disease shows it to be essentially a chronic disease with numerous relapses as its usual feature. The present state of sanitation and hygiene in this country affords additional scope for reinfection. The results of treatment of amœbic dysentery even where carried out very assiduously, as in the army, have proved unsatisfactory. In a general and teaching Government Hospital as Sir Jamsetji Jeejeebhoy Hospital the treatment of amoebic dysentery amounts to 6 to 10 injections of emetine hydrochloride and an astringent mixture. There is no follow up with local treatment partly because the drugs are not available in the hospital and partly because of the necessity of the quick turnover of the patients due to paucity of beds; neither is there a laboratory check-up before discharge. In spite of this sad state of affairs the proportionate incidence of amoebic hepatic abscesses seems insignificant. This fact was well recognised by the early observers. Thus, in the Indian Army "man for man relative liability of the European soldier and the Indian soldier was as 95.2 to 4.8" (Manson Bahr[12]). The same is observed in the civil population; thus in the ten-year period 1939 to 1949, in the Jamsetji Jeejeebhoy Hospital there were 836 recorded cases of amoebic dysentery and for the same period there were only 33 cases of amoebic hepatic abscess. The proportion of amoebic dysentery to total medical admissions was 2.7 per cent while that of amoebic hepatic abscess was 0.11 per cent. It may partly be accounted for by the fact that most of the cases of amoebic hepatitis or presuppurative stage of liver-abscesses (Roger[20]) are recognised and treated early by the use

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§ Paper read before the Staff Meeting of the Jamsetji Jeejeebhoy Group of Hospitals and Grant Medical College, Bombay, February, 1949.

of emetine. Unfortunately the statistical figure for such cases of amoebic hepatitis in this hospital is not available in the records.

The present paper is intended to give the statistical analysis of these 33 cases of amoebic liver abscess.

The common association of liver abscess with amoebic dysentery was proved by Rogers[20] as early as in 1902; and since then the amoebic liver abscess has not remained "tropical liver abscess" as it was labelled in the early days. The incidence of amoebic dysentery and the occurrence of liver abscesses is reported from all parts of the world. Even before the last War it was an endemic disease in the British Isles. As early as in 1891 Councilman and Lafleur[6] in the United States found that in 1429 cases of clinical amoebic dysentery 21 per cent showed hepatic abscess. Craig[7] analysed 1529 cases of amoebic dysentery that came to autopsy and found that 40 per cent of these showed liver abscesses. Brown and Hodgson[3] state that in the north temperate zone, of dysentery cases 2 to 3 per cent show liver abscesses. Kern[10] mentions that of 9696 cases of clinical amoebiasis collected from the literature, hepatic abscess was present in 4.86 per cent. Berne deprecates the retention of the term "tropical liver abscess" in some text books as the term is misleading and proves an obstacle to the early diagnosis of amoebic liver abscess in non-tropical countries. During the ten-year period the incidence of abscess was almost equally distributed, the maximum incidence was shown in 1944. The average per year comes to 3.3 cases. Table 1 shows the yearly incidence.

TABLE 1—*Yearly Incidence.*

1939	1940	1941	1942	1943	1944	1945	1946	1947	1948
3	2	1	2	3	8	2	4	2	6

The amoebic liver abscess being a border-land condition between medicine and surgery, in the present series 26 cases were admitted to the medical units, and 7 to the surgical.

AGE AND SEX

The maximum age-incidence is generally in the third and fourth decade. In the present series 19 cases (57%) were between 21 and 40 years; the youngest patient being 13 years of age. Table 2 shows the details of age incidence.

TABLE 2—*Age Incidence.*

Below 20 yrs.	21-40 yrs.	41-60 yrs.	60 yrs. onward.
3 11%	19 57.5%	10 30%	1 3%

The sex incidence also is characteristic, the amoebic hepatic abscess being very rare in females. This fact is universally accepted and the low incidence of amoebic hepatic abscess in European females in India in contradistinction to high susceptibility of European males was remarked upon by all early observers. Brown and Hodgson[3] had 4 females in a series of 35, Berne[2] had 5 females in a series of 74. In the present series of 33 there was no female patient. The non-susceptibility of females seems common to European as well as Indian women. Cameron[5] quotes one case in an Indian female patient.

Previous Illness and Personal History:—

The history of a previous attack of dysentery was obtained in 12 cases (36%) only. It is now well recognised that liver abscess may come on without any obvious previous history of dysentery. The attack may be ignored as a simple diarrhoea. In about 7 to 10 per cent of cases of intestinal amoebiases there is persistent constipation. In Berne's 74 cases, 30 had diarrhoea and 6 complained of constipation.

There was history of trauma to the chest in 2 cases in the present series. Berne[2] mentions 3 cases out of his 74 which were precipitated by trauma to the chest.

The history of habitual alcoholic ingestion was obtained in 8 cases (24%). Rogers[20] believes that in Europeans in the Tropics alcoholism plays a prominent part in precipitating the liver abscess or aggravating it. DeSilva[8] from Ceylon analysing 200 cases of hepatic amoebiasis was in agreement with Rogers as regards the part played by alcoholism in liver abscess.

In the present series, 18 were vegetarians and 15 were non vegetarians and the type of food seems to affect very little the course of hepatic abscess.

MODE OF ONSET.

The mode of onset is commonly a gradual one. Rogers mentions that in 103 cases of liver abscess in Europeans the duration of symptoms before admission was over one month in 51 per cent of the cases. In the present series the duration of symptoms before admission ranged from 8 days to 1 year, the average being 61 days. The mode of onset was gradual in 28 cases (84%) and sudden in 5 (15%). In 74 cases Berne found that in 58 per cent it was an acute and a severe disease.

The commonest presenting symptoms are fever with or without rigor, pain in right hypochondriac area, cough, loss of appetite, loss of weight and frequency of stools. In Ochsner's[15] 102 cases fever was present in

69.8 per cent of cases. In the present series the pain in right hypochondrium was present in 90 per cent and fever in 78 per cent.

The details of incidence of symptoms is given in Table 3.

TABLE 3—*Incidence of Symptoms.*

Symptom		Cases	%
Fever	with rigor.	18	54%
	without rigor	8	24%
Pain	Rt-hypochondrium	30	90%
	Rt. chest.	8	24%
	shoulder	3	9%
	shoulder and hypochondrium	3	9%
Frequency of stools.		3	9%
Cough		8	24%
Loss of weight		3	9%
Oedema feet		3	9%
Loss of appetite		3	9%

PHYSICAL SIGNS.

On clinical examination the enlargement of the right lobe of the liver is the commonest physical sign; rarely, the left lobe alone or along with the right lobe may be involved. Cameron[4] mentions one case seen by him in an Indian female where the abscess was in the left lobe only. The secondary pulmonary physical signs as impaired movement, diminished T. V. F., impaired note at the right base are also quite common and unless that possibility is kept in mind it might lead to an erroneous diagnosis. The liver abscess may present itself as a case of pleurisy with effusion. Berne[2] mentions that in his series of 74 in 33 per cent, the abdominal symptoms and signs were absent and the pulmonary physical signs were dominant. According to mode of onset and the presenting symptoms he describes four clinical syndromes of liver abscess (1) acute costal margin syndrome, (2) chronic costal margin syndrome, (3) acute pulmonary syndrome, (4) chronic pulmonary syndrome. The names of the syndromes given are self explanatory and need not be discussed.

In Ochsner's[14] 102 cases the enlargement of liver was present in 65.7 per cent. In the present series the enlargement of liver was present in 31 cases (93%). Lung signs were present in 18 (54%), splenic enlargement in 6 (18%), and jaundice with bile-pigments in the urine in 2. The association of intense jaundice with liver abscess is rather rare and if present seems to augur worse prognosis. Reddy and Rangam[19] report such association in 2 cases from the autopsy records. In the present series one case with jaundice recovered and one died.

Table 4 gives the details of incidence of physical signs.

TABLE 4—*Physical Signs.*

Physical Signs	cases	%
Hepatic enlargement	Right 30	90%
	Left 1	3%
Splenic enlargement	6	18%
Pulmonary Signs including Pleural pleurisitic effusion.	18	54%
Jaundice	2	6%

INVESTIGATIONS

The leucocytic count was done initially in 31 cases. There was leucocytosis in 21. The count was normal in 6 and there was leucopenia in 4 cases. No follow-up leucocytic count was done in any case.

The patients were examined radiologically in 29 cases. In 11 cases the right dome of the diaphragm was abnormally high and movements were sluggish concurrently. In 18 cases the movements of the diaphragm were sluggish or absent without the high position of the diaphragm.

Diagnostic aspiration was done in 21 cases. The pus, on culture, was sterile for pyogenic organisms in 19 and 2 specimens were positive for streptococci and staphylococci.

In no case air replacement or lipiodol instillation into the abscess cavity after aspiration was done.

The stools were examined in 16 cases only and they were negative for cysts and vegetative entamœbæ in all cases.

The importance of leucocytic count in diagnosis and in following the progress of amœbic hepatitis and abscess was well stressed by Rogers.[20] He found that there was a constant leucocytosis in hepatitis and abscess and as the patient improved with emetine injections the leucocytic count returned to normal. In the treatment of liver abscess by emetine injections and repeated aspirations serial leucocytic counts are useful. Pfanner[17] reporting analysis of 18 cases found that if in spite of the repeated aspirations and emetine injections the leucocytosis persisted it meant that either there was still retention of pus in the aspirated abscess or probably there was another abscess which required further needling. It is maintained that 30 to 40 per cent of amœbic hepatic abscesses are multiple (Rogers,[20] Palmers[16]). To find out the extent of the abscess cavity and the amount of pus retained and also in the assessment of the progress of a case, air replacement in conjunction with radiological examination was used by Ochsner and DeBakey[15] and by Cameron and Lawler. After aspiration of as much pus as possible air was injected till the patient complained of pain in the shoulder, or if there was no pain air to the extent of half the volume of pus removed was injected and serial radiological examinations in different positions were done. This was found very useful in 12 cases of amœbic hepatic abscess by the latter. This simple method obviated the use of heavy and irritating material as lipiodol or thorotrast.

STOOL EXAMINATION

The repeated examination of stools in cases of liver abscess is very necessary. It has been amply proved that hepatic amœbiasis is invariably secondary to the intestinal infection. In the post-mortem room the amœbic liver abscess is associated with concurrent ulcers in the intestines in the majority of cases. Brown and Hodgson[3] found amœbic abscess on proctoscopic examination in 7 out of 17 cases of liver abscess. If only the liver abscess is treated and the primary intestinal amœbiasis is ignored there is every possibility of the recurrence of the abscess as it is well-known now that though emetine injections are useful in hepatic amœbiasis the intestinal amœbiasis is often resistant to parenteral administration of emetine alone.

COMPLICATIONS

The main complication of liver abscess consists in its bursting into one of the adjacent serous sacs. Sometimes this gives rise to apparent considerable relief by evacuating the pus through the lungs and bronchi but at the same time it might make the patient a chronic invalid. In the present series 2 cases burst into the lungs through the diaphragm and pleura, five cases pointed superficially through the chest wall or the anterior abdominal wall, one had pulmonary tuberculosis in addition to liver abscess, one died of peripheral cardiac failure. One perforated in the subphrenic area. There was neither a burst nor any sympathetic effusion in the pericardium. Kern mentions 22 proved cases of amœbic pericarditis in the literature and gives a report of one additional proved case with autopsy-report in a Negro patient. Purcell[18], Royster *et al.*[21] Sing[22], Laha[11] described cases of pericarditis associated with amœbic liver abscess. These reports are instructive and I feel that some cases of pericarditis with effusion with enlargement of liver and associated pleurisy which are commonly labelled nowadays as Pick's syndrome or polyserositis may belong to the group of amœbic pericarditis. This type of case is quite common nowadays in our fortnightly clinical meetings. Walters[23] *et al.* describe two cases of subdiaphragmatic perforations simulating perforated peptic ulcers.

Out of 8 cases Pfanner[17] observed that 3 ruptured in the subphrenic area, 1 in the pleural cavity and 1 in the peritoneum.

TREATMENT

The treatment of amœbic liver abscess has mainly remained the same as was first enunciated by Rogers in 1922 and consists of repeated aspirations and administration of emetine parenterally. Rogers maintained that most of the amœbic liver abscesses were sterile; thus 86 per cent of his 87 cases were sterile on first opening. It is thought that only 8 to 10% of the amœbic liver abscesses are secondarily infected before they are opened and in such infected cases the use of the sulpha group of drugs and penicillin is reported nowadays with very good results. Alport and Ghaliougui[1] report two such results with sulpha drugs in addition to emetine and aspiration. Noth and Hirshfield[13] and Kark[9] describe one case each who had penicillin in addition to the usual measures, with remarkable results.

In the present series of 33 cases, 32 had parenteral emetine—26 of them had ½ gr. of emetine per day for 8 to 10 days and 6 of them only had 1 gr. of emetine daily for a similar period. Repeated aspirations were done in 19 and open operation in 9. In 4 cases recently penicillin was given in addition to the usual measures.

In no case sulpha group of drugs was used. It is known that emetine if given in bigger doses and for prolonged period, gives rise to toxic effects but unless the drug is given in optimum dosage the effect may well be nullified. In all 32 cases who had emetine there was not a single mention of the toxic effects on the heart; it may be claimed that this was because in the majority of cases a smaller dose was used. I personally feel that gr. ½ of emetine in a liver abscess or suspected liver abscess is an insufficient dose in a patient who is at rest in hospital and many writers have voiced the same opinion; with smaller doses of emetine the heart remains normal but the probability is that the patient may die of liver abscess. Probably the cardiologists will be better able to tell us the toxic effects of emetine observed by them clinically and by the aid of the electrocardiogram.

In the Army I had occasion to advise emetine parenterally in a large number of patients. I always used the bigger dose, *i.e.*, 1 gr. daily and I do not remember any case dying of toxic effects of emetine. It may be argued that there I was dealing with a selected population, but even in civil practice, in a big hospital like ours, for the last 6 years I have hardly seen 1 or 2 cases of extra systoles produced by parenteral emetine in optimum doses. Further, before penicillin came in it was the practice to inject emetine locally actually in the abscess cavity after aspiration. In no case was such a procedure used in the present series. No patient had follow up local treatment for intestinal amœbiasis; probably familiarity with the disease makes us treat it contemptuously. Here again it is true that the drugs for local treatment of intestinal amœbaisis are generally not available in the hospital. I plead that concerted effort be made by the medical staff in obtaining regular supply of such essential and useful drugs from the hospital authorities.

RESULTS

Out of 33 cases, 23 were relieved of their symptoms; one got discharged against medical advice and there were 9 deaths in the series (27%). Going into details out of 26 medical admissions 6 died (23%) and out of 7 surgical admissions 3 died (42%). Our mortality figures are definitely high as compared with those of others. Rogers[20] mentions 56.8% mortality for open operation and 14.4% for emetine and aspiration. Ochsner[14] gives the detailed figures as follows: –

16	cases of transpleural approach	25 %
14	,, of rt. rectus incision	21.4%
7	,, incision and drainage over the most-dependent part	14.2%
9	,, incision and retroperitoneal approach	11.1%
24	,, aspiration and emetine	4.1%
70	cases	14.2%

Rogers[20] figures deal with both European and Indian patients collectively. It is a fact that the Indian patient is a poor specimen physically as compared with the European patient and more so the South-Indian; nutritional deficiencis are very common and practically there is no reserve power to fight the disease. The Indian patient traditionally comes at a very late stage to the hospital and is rather over anxious to get out of the hospital as soon as possible. These factors probably account for the high mortality. Unfortunately I cannot give you the details of surgical procedures used by the surgical colleagues and their separate mortality as the notes of the operations were very brief.

The duration of stay in the hospital ranged from 3 days to 102 days—the average being 30 days.

SUMMARY

Thirty three case-records of amœbic hepatic abscess are analysed statistically for finding out the incidence of symptoms, physical signs, complications and results of treatment.

The incidence of hepatic abscess compared with the prevalence of amœbic dysentery is insignificant.

The mortality in this small series was 27%.

The importance of the follow up treatment of primary intestinal amœbiasis in hepatic amœbiasis is stressed.

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LIVER BIOPSY

J. G. Parekh

Biopsy studies have become very popular, especially tumour biopsy, In recent times a large number of articles have appeared in medical literature about one or other method of biopsy of one or other organ.

Liver disease is very common. Of late, great attention is being paid to the structural changes in the liver which are a result of malnutrition, infectious hepatitis, etc. Attempts are being made to study and correlate histological alterations occurring in the liver during the various phases of disease during life. The functions of the liver are diverse. Hence the number of functional tests are numerous and no single efficiency test of liver function can be considered to be entirely satisfactory. Further these tests by themselves do not help much in the diagnosis of a case. Under such circumstances it was felt that if the liver tissue itself could be removed with ease and safety, one might actually see the structural changes in the liver in various diseased states and during various phases of the same disease. This knowledge might change our present concept of some of the diseases. In perplexing cases, by providing a diagnosis, liver biopsy would render exploratory laparotomy unnecessary. In the beginning of this study we came across such a case where laparotomy was abandoned because the liver biopsy showed evidence of malignancy. The work was then extended to other cases, and histopathological study of tissue was found to be quite useful in some of the obscure cases.

Liver biopsy is not a new operation. Aspiration of the liver has been known for many years. One of the earliest reports is that of Roberts[8] in 1883, who used this method in the treatment of hepatic suppuration and hydatid disease. The credit for the earliest liver biopsy for purposes of a diagnosis goes to Lucatello[7] (1895), but he did not employ the modern methods of fixation and staining of the tissue. With the development of these methods tissues can be studied histologically. A report on material from 100 livers thus obtained and studied was made by Bingle[2] in 1923. It is generally recognised that the work of Inversen and Roholm[5] brought about a renewal of interest in this subject. Many studies on this problem have been carried out subsequently but instead of going into the details of these, the data are presented in a tabular form.

TABLE 1—SUMMARY OF LIVER BIOPSY STUDIES BY VARIOUS AUTHORS

Author's Names.	Year	Number of Biopsies	Method	Approach	Mortality	Hemorrhage	Peritonitis	Failures
Lucattelo	1895	Not known	Aspiration	Not known	Not known	Not known	Not known	Not known *
Schupfer	1907	"	"	"	"	"	"	" †
Bingel	1923	100	"	"	2	2	0	"
Oliver	1926	140 (Including 100 of Bingel)	"	"	3 (includes those of Bingel)	2	1	"
Frola	1935	66	"	"	0	0	0	"
Huard, May & Joyeux ..	1935	163	"	"	0	0	0	"
Iversen and Roholm ..	1939	160	"	Transpleural	0	0	0	10-15 %
Baron	1939	48 (Subsequent not known)	"	Abdominal	1 (Occurred subsequent to the 48 Biopsies)	1	0	Not known
Shiray, Fessinger & Roux..	1941	41	"	"	0	0	0	22%
Tripoli and Fader ..	1941	14 (Total no. not given).	Punch with Vim Silverman needle	"	0	0	0	Not known
Dible, McMichael & Sherlock	1943	126	Aspiration	Transpleural	2	5	0	10%
Hatieganu Spatchez Radu and Ma Cavel	1943	45	Not known	"	0	0	0	Not known
Von Beck and Haex ..	1943	200	"	"	0	0	0	Rarely
Hoffbauer, Evans and Watson	1945	85	Punch with Vim Silverman Needle	With peritoneoscopy—abdominal.	0	1	0	30-140%
Sherlock	1945	265 (Including 126 in 1943)	Aspiration	Transpleural	None since 1943 biopsies.			2% in 138 cases
Wahi	1946	No. not stated	Punch with Silverman needle.	Transpleural	1 (Died of shock)	0	0	0
Schiff *et al.*	1946	75	"	"	0	0	0	Not known
Present Series	1947	100	Mainly punch with Silverman needle. Occasionally Aspiration	Transpleural and Abdominal	0	0	0	15%
Total ..	Over	1402			6	9	1	

* Did not employ fixation and staining. † Employed methods of fixation and staining.

METHODS

There are several methods of obtaining liver tissue during life: —

During laparotomy a piece of liver can be removed. With the co-operation of our surgical colleagues we obtained several specimens in this way. This method is, however, impracticable for routine use. Methods which would save laparotomy are to be preferred. Such methods are :—

Postero-lateral, transpleural, transdiaphragmatic aspiration method as practised by Iversen and Roholm[5] or as modified by Sherlock[9]. This method has been described in detail by the latter and was tried by me in a few cases.

Baron[1] employed a similar aspiration method but used an abdominal approach below the costal margin. This route was also tried in some cases.

Tripoli and Fader[10] employed Vim-Silverman needle for performing liver biopsy. They employed the abdominal route.

Hoffbauer *et al.*[4] combined peritoneoscopy with liver biopsy, the specimen being obtained by a special forceps attached to the peritoneoscope. This method has the advantage of visualising the liver surface and selecting a proper biopsy. It has, however, been stated that the tissue thus obtained is only subcapsular and may not truly depict the changes in the substance of the liver. On account of this objection the forceps was replaced by Vim-Silverman needle.

Frank Ellis[3] has been using a mechanical drill attached to the aspirating needle to obtain tissue for biopsies.

In this study the Vim-Silverman needle has been employed mostly. Both the abdominal and the transpleural routes were utilised; the latter more frequently than the former. This method appears to be better than others because its use is not attended with the degree of trauma and maceration of the tissue incidental to aspiration methods and because a definite column of liver tissue free from blood can be obtained. This can be studied histologically more satisfactorily, than the few cells obtained by aspiration. Thus the diagnosis is easier to make and more accurate when made.

DESCRIPTION OF THE NEEDLE

The needle consists of three pieces (1) a trocar an outer wide bore needle 13¾ cm. long 2 mm. wide with a bevelled edge, (2) an obturator which fits into the trocar, and (3) a narrow forked needle 15 cm. long which when fully inserted into the trocar projects beyond the tip of the latter.

As it is desirable that this method of study be widely employed the following details are given even at the risk of repetition.

SELECTION OF THE PATIENT :

The following type of cases should be avoided as far as possible :—

(i) Moribund cases.-No useful purpose would be served in such cases.

(ii) Cases with a marked bleeding tendency as judged by (a) occurence of bleeding (b) marked increase in bleeding time, coagulation time or prothrombin time. In two cases where there was marked epistaxis, but the bleeding and coagulation time were normal, biopsy was ventured without adverse effect.

(iii) Cases with marked congestion of the liver.

PREPARATION OF THE PATIENT :

It is desirable to obtain cooperation from the patient. It is necessary to determine:

(1) The blood group and to keep readily available a sufficient quantity of suitable blood.

(2) Bleeding and coagulation time.

(3) Prothrombin time.

The patient receives two days before and after the operation calcium lactate orally or calcium gluconate parenterally. If he is jaundiced 5-10 mg. Vitamin K are given parenterally or orally depending on whether the jaundice is non-obstructive or obstructive.

TECHNIQUE

The biopsy is performed by the bedside in the wards. Preliminary morphine and atropine was given in the first few cases but subsequently it was used only in those patients who were apprehensive. Those who did not get it were not worse of.

The patient lies flat in bed or preferably with a slight tilt on the right brought about by placing a small pillow under his left-side. His right-side should be as near the edge of the bed as possible. His right arm is drawn up above his head.

The liver is percussed between the anterior and posterior axillary lines, and the dullest spot in the 9th or the 10th intercostal space is selected. The preliminary cleansing of the skin as for surgical operations is carried out. With a fine long needle attached to a syringe containing 2-3 cc. of 2% novocaine solution, the selected site and the whole of the track upto the capsule of the liver are infiltrated. It was considered preferable to make a small nick in the skin with a scalpel at the site of selection. The Vim-Silverman needle is introduced through the anaesthetised track upto the surface of the liver. This can be made out by a feeling of a slight resistance. . The needle is now entered to a depth of about 1 cm. into the liver substance. The needle starts swinging with respiration. The obturator is withdrawn and the inner split needle introduced into its place and pushed on to its full length beyond the outer needle. This would punch out a column of liver tissue between the two prongs of the split needle. Now the outer needle is pushed on further so as to hold the two prongs of the forked needle containing the liver column together. It is then rotated in order to cut out the base of the column of liver tissue. Both the needles are now withdrawn and the wound sealed with collodion or Tinct. Benzoin Co. A little oozing out of blood from the needle after withdrawal of the obturator need cause no alarm, though on the first occasion the biopsy was abandoned on account of this.

In those cases where the liver is definitely enlarged the anterior route is followed. The patient lies flat in bed; a small pillow may be inserted behind the small of the back. The point selected is lateral to the tip of the 9th costal cartilage and midway between the costal margin and the lower edge of the liver. This area on percussion should be dull.

In some cases with left lobe enlargement the needle is introduced in the epigastric region and directed upwards and to the right. If the liver is very mobile or easily ballotable it is fixed by hand by an assistant. The rest of the procedure is more or less the same as described above. If a nodule is felt, this should be selected for biopsy. The material obtained is transferred to a fixative (10% formalin saline or any other suitable fixative) and sections cut and stained with haematoxylene-eosin; as with any tissue for histological study.

AFTER-CARE OF THE PATIENT

After the biopsy the patient is confined to bed for 24 hours. The pulse is recorded 2 hourly for the first 4 hours and then 4 hourly. Arrangements are kept ready for an immediate transfusion, should it become necessary.

Ordinarily the procedure is attended with very little pain or discomfort but dull aching pain, aggravated by deep breathing is often present. For this a mild analgesic like aspirin would suffice. Some of the patients complained of pain in their right shoulder.

Though the patients are asked to remain in bed an occasional patient was seen moving about without any harm having come to him. This suggests the possibility of carrying out the investigation even in the out-patient department as is done at some places for splenic puncture.

DIFFICULTIES AND DANGERS OF BIOPSY

1. Biopsy should not be performed at random and without proper preparations. Cases must be selected and properly prepared. From Table 1

it can be seen that there have been 6 fatalities in about 1,500 biopsies which works out at about 0.4%. Sherlock[9] has shown a mortality of 0.67% but she had inadvertently computed the mortality in cases of Bingel and Oliver separately, whereas, they represent the same cases. Further some of the biopsies included in Table 1 have not been included by Sherlock[9].

2. The most important, dangerous and often fatal complication is haemorrhage. It is stated by various authors that haemorrhage is more frequent when the intercostal route is employed, the reason being that the needle gets fixed between the ribs and not being allowed to move freely with movements of the liver, produces a longitudinal rent in the liver. Of about 1,500 biopsies done by the authors listed in Table 1, 9 cases had haemorrhage (0.6%). Sherlock[9] has shown that haemorrhage occurred in 5 cases out of 78 when a 2 mm. bore needle was used and no mortality in 74 cases where a thinner needle was used. In cases coming to autopsy on whom liver biopsy was performed earlier, it was difficult to find out the site of puncture. At times the spot was a little darker than the rest of the liver tissue. There was no haemorrhage to be seen on the surface of the liver.

3. Infection is another possible danger. This may occur due to:

(1) Introduction of sepsis from the outside.
(2) Perforation of the gastro-intestinal tract and peritonitis.
(3) Spread from an existing abscess cavity.

4. There is only one case in the literature in Oliver's series where death resulted from peritonitis. In one case—Hoffbauer *et al*[4]. found the mucous membrane of colon in the sample but nothing adverse happened to the patient. Occasionally a slight rise in temperature may occur as after any minor surgical operation. The patient sometimes complains of weakness after the puncture.

5. Failure to obtain liver tissue is not uncommon. Various authors have reported failures ranging from 0 to 40%. The writer met with failures in about 15% of the cases. In the early stages the failure was due to lack of experience and the rate of failure diminished with practice. In the beginning the needle used was too short, with the longer needle the failures have been very few.

The greatest number of failures were obtained in cases of ascites, 10 out of the 15 failures. In these cases, fluid often came out of the cannula thus showing that the needle had not reached it. It was difficult to pierce the cirrhotic liver which often moved away because of the fluid in the abdomen. Tapping the abdomen and removing the fluid previously and then tilting the patient to the right made it easier to reach the liver.

6. If the skin was not nicked sometimes the needle used to get blocked and no material was obtained or a bit of skin or muscle by itself or along with the liver tissue was obtained especially if the obturator was not introduced fully.

7. Another difficulty experienced was that the column of liver tissue during its transference from the groove of the forked needle to the fixative often got broken.

8. With the shorter needle sometimes very little liver tissue was obtained and in such cases the histological diagnosis was often not possible.

It is possible to repeat the operation in case of failure to obtain liver tissue or where it is desired to study the case from time to time. In a few cases biopsy was done twice on the same patient and in one case on four different occasions.

Liver biopsy was performed in the following types of cases:

TABLE 2—*Distribution of Case material.*

Acute Hepatitis		
	Infective hepatitis	34
	Spirochaetal jaundice	2
	Arsphenamine jaundice	2
Cirrhosis of liver		30
Malignancy of liver		8
Kala Azar		2
Obstructive jaundice		1
Blood diseases	Anaemia	3
	Leukaemia	1
Amyloid disease		1
Miscellaneous		16
		100

UTILITY OF LIVER BIOPSY

The question naturally arises about the utility of this procedure. New methods of diagnosis are being introduced from time to time, majority of them being ultimately discarded. Is liver biopsy a real advance on the methods already available and would it stay permanently as a diagnostic procedure ?

It would be pertinent to argue that examination of a small bit of liver tissue may not show what may be happening to the rest of the liver. This is quite true in some cases. There are two types of liver affections, one in which the liver is affected uniformly as in various types of hepatitis and the other, in which the lesions are scattered as in malignant metastases. In the former, the histological picture of the tissue obtained by biopsy would represent the changes in the rest of the liver; in the latter it all depends on luck, diagnosis is possible only if one happens to strike at the lesion. Though our experience is limited it is felt that positive information is obtained more frequently in the latter group of cases.

A few cases are here reported to show the utility of this procedure. The cases are given in brief, mentioning only essential points.

MALIGNANCY OF LIVER WITHOUT JAUNDICE.

In cases of enlarged liver without jaundice, laparotomy may have to be resorted to for the sake of diagnosis. If on laparotomy malignancy of the liver is found, nothing further could be done. · If in such cases a liver biopsy could prove the diagnosis, laparotomy would be unnecessary.

Three case reports are cited here to show how biopsy was helpful in making a diagnosis in this group of cases.

Case 1.

A Javanese male aged about 35 years, was admitted for bleeding from the nose, and abdominal pain.

He was well-built but emaciated. A hard gland was found in the anterior triangle of the neck on the right side. The right sternoclavicular joint was enlarged and tender. The liver was enlarged 3 fingers breadth and tender; the surface was irregular and nodular. The spleen was not felt. The other systems did not reveal any abnormality.

Investigations : Blood : moderate anaemia with a leucocytic count of 15,500 p. cu. mm. Kahn test negative. Stool : N. A. D. Urine : N. A. D. Sputum : N. A. D. Screening of the chest : Lungs—bilateral catarrh. Heart—slightly enlarged, aortic knuckle prominent. X-ray of the right sterno-clavicular joint : ? Tubercular caries of the joint.

In view of the enlarged tender liver and pyrexia the patient was given emetine but did not respond. A laparotomy was thought of. In the meanwhile the biopsy of the gland and of the liver were performed and malignancy was detected in both tissues. Later the patient died and on postmortem examination it was revealed that there was a very tiny primary growth in the bronchus with secondaries in the liver, cervical gland and right sternoclavicular joint.

Case 2.

Female, aged 40 years, was admitted for swelling of abdomen and legs, breathlessness, pain left side of the chest and cough. The trouble started 4 months back with cough. This was followed by pain in the left side of the chest and later by swelling of abdomen. For the last 10 days there was oedema of the feet. Occasionally she got fever. She was poorly built, ill nourished with pale skin, nails and mucous membranes. The lymph glands were not palpable. Free fluid was present in the abdomen. Spleen and liver were not felt, and there was effusion in the left pleural cavity. The heart sounds were feeble and nothing else was abnormal. Blood pressure was 120/90 mm.

The deep reflexes were not elicited but otherwise the examination of the nervous system was normal. After tapping the liver could be felt to be enlarged 3 fingers, firm and irregularly nodular and several other irregular masses were felt in the peritoneum. Later the spleen also became palpable. Investigations : Blood : R. B. C. 2.3 m. p. cu. mm. Hb. 6 G. per cent. W. B. C. 4200 p. cu. mm. Kahn Test: negative. Blood urea: 59 mgm. per cent. Plasma proteins: total 5.77 G. per cent. albumin: 2.84 G. per cent. globulin : 2.97 G. per cent. Sputum : negative. Urine N. A. D. Stool : negative. Chest screening : Massive pleural effusion left side ; Ascitic fluid : exudative in character, at first straw coloured, later hæmorrhagic. Pleural fluid : exudative in character and hæmorrhagic.

Liver biopsy on 25/1 :—no evidence of malignancy. Liver biopsy on 12/2 :—metastasis in the liver. Postmortem at a later date confirmed the findings.

Comment:-When the patient was first admitted the probable diagnosis was cirrhosis of liver. In the alternative, due to exudative nature of the fluid the possibility of tuberculosis was entertained. When the liver became palpable malignancy was naturally thought of.

The interesting point in this case is that the first biopsy did not reveal the presence of malignancy. It was only repetition of biopsy which gave the diagnosis.

Case 3.

Another similar case of malignancy without jaundice. Mrs. M., age 55 years, was admitted for abdominal pain and irregular pyrexia, for 3 months. On examination the patient was found to be fairly built but poorly nourished The skin and mucous membranes were pale. The abdomen was bulging in the right hypochondrium and epigastric region and veins were visible on the surface. The liver— was irregularly enlarged, nodular and hard. The spleen was not palpable. The other systems were normal. Blood showed moderate anæmia with leucopenia. Bleeding time and coagulation time were normal and the icterus index was 8. Van den Bergh : indirect positive Blood W. R. negative.

The diagnosis lay between hepar lobatum, gummatous liver, and malignancy. Exploratory laparotomy was withheld pending biopsy. Patient had severe epistaxis and biopsy was postponed for 24 hours. During puncture it was found that the needle met with great resistance in the beginning which suddenly gave way and when the trocar was removed thick curdy-looking, blood stained material welled out. Some more material was aspirated. This material did not look like that of liver abscess.

On sectioning amongst masses of blood clots two clumps of cells with irregular outlines and hyperchromatic nuclei resembling malignant cells were seen. This gave the diagnosis. The patient expired after about 3 months.

Comment: A definite diagnosis was arrived at after the biopsy.

ASCITES

Patients having ascites form another group in which biopsy is helpful. Ascites is due to many causes. As diagnosis is not always possible biopsy of the liver may give a correct diagnosis. In patients with ascites liver biopsy revealed at times (1) malignancy of the liver (case already cited); (2) cirrhosis of the liver; (3) post-hepatitis repair, subacute nodular cirrhosis; (4) focal necrosis of the liver, as in tuberculosis of peritoneum; (5) fatty changes in the liver as in anaemia.

Male, aged 35 years, was admitted for ascites and oedema of feet. The ascites appeared first, its duration was 2½ months. Oedema of the feet appeared later and its duration was 1 month. There was history neither of alcoholism nor of eating spicy food nor of venereal disease. He was a thin individual, pale looking with pale mucous membranes. The tongue was coated. Ascites was present but the veins on the abdomen were not distended. The liver was palpable 1 finger below the costal margin, but the spleen was not felt. Other systems did not reveal any abnormality. *Investigations* : urine and stools were normal. Blood : R. B. C. 2.62 m.p. cumm. Hæmoglobin : 9.5 G. P. C; V : 32 parts p. 100. W. R. : negative. Bleeding and coagulation time was normal. The ascitic fluid was a transudate. Intravenous hippuric acid test : 0.37 G. Icterus Index : 10 units. Van den Bergh test : indirect positive. Prothrombin time : 28.5 sec. Plasma proteins : total 5.8 G. per cent. albumin : 2.8 G. per cent. globulin 3.0 G. per cent. Blood urea : 49.5 mgm. per cent. Liver biopsy : Cirrhosis of liver.

Comment: In absence of positive findings such as enlarged spleen, distended veins, haematemesis etc., the diagnosis of cirrhosis could not be made but biopsy revealed the presence of cirrhotic state. This patient made a fairly good recovery on a high protein, low fat diet.

Post-Hepatitis Repair: Patient, age 60 years, was admitted for ascites. The swelling of abdomen was of 1 month's duration and breathlessness of 7 days. Fever came off and on. The cough was worse at night. He was addicted to alcohol and was a heavy smoker. Well built, fairly well nourished with pink mucous membrane and a moist and clean tongue. There was free fluid in the abdomen, and the viscera could not be felt, but after tapping the spleen could be felt. The spleen enlarged progressively during the patient's stay in the hospital. Rales were heard at the lung bases. Other systems were normal.

Investigations. Blood: R.B.C.: 4 m. Hb.: 14 G. W.B.C.: 4330. p. cumm., Blood W. R. negative. Plasma proteins : Total 6.5 G. per cent. Albumin 3.33 G. per cent. Glob. 3.17 G. per cent. Blood urea : 39 mgm. per cent. Bleeding and clotting time normal. Urine N.A.D. Later hæmaturia. Stool N.A.D. Later bleeding per rectum.. Sternal puncture : No. L.D. bodies. Ascitic fluid exudative in character. Liver biopsy : Many liver lobules were seen, there was no necrosis but cells looked cloudy and granular. There was congestion of central vein but no inflammation of its wall. There was no increase of bile canaliculi. Histocytic and round cell infiltration was seen in portal areas and in between liver cells—at some places dense enough to suggest a scar. Late repair after infective hepatitis.

Comment: This case was diagnosed as cirrhosis of the liver, the biopsy revealed late repair after infective hepatitis.

In another very similar case in a young patient the diagnosis lay between tuberculosis of the peritoneum and cirrhosis. Liver biopsy showed focal necrosis and no cirrhosis. Later this case showed definite evidence of tuberculosis.

PRE-CIRRHOTIC STATES

Liver biopsy may prove of value in pre-cirrhotic states.

In alcoholic cirrhosis of the liver it is recognised that before the actual cirrhotic process occurs there is fatty degeneration of the liver cells. If a patient is detected in this state it may be possible to arrest the progress of the case and prevent the occurrence of cirrhosis by adequate treatment. Similarly in cases of malnutrition, especially protein deficiency cases, cirrhosis is likely to develop. If, however, the liver of such patients shows that the cirrhotic process has not yet started then one can hope for complete recovery. The third type of case is one in which the patient is suffering from splenic anæmia or "Banti's disease". It is known that these patients ultimately develop cirrhosis of liver. If splenectomy is performed in such a case before the liver is affected, the further progress of the case may be arrested. Liver biopsy would indicate whether cirrhosis has developed or not.

ILLUSTRATIONS

1. A young girl aged 11 years was brought for enlargement of the abdomen. The history dates back to 3 years when progressive enlargement of the left side of the abdomen was noticed. During this period she had two attacks of hæmetemesis. She became progressively anæmic. On examination she was rather undersized for her age, pale looking. The abdomen was prominent more on the left side, veins on the abdomen visible but not distended. There was no free fluid in the peritoneal cavity. Spleen was enlarged upto the umbilicus and the liver was felt just below the costal border. Other systems were normal. Blood examination revealed a hypochromic anæmia with leucopenia. R. B. C. : 3.3 mp. p c. mm. H6:40% (Sahli) ; C. I. : 0.6, R. C. D. 6.8 G. (Halometric) W. B. C. : 3050 p. c. m.m. Other investigations were normal. Diagnosis ; splenic anæmia. Liver biopsy was requisitioned to exclude cirrhosis. On not finding any evidence of cirrhosis splenectomy was advised.

2. A young man aged 36 years who was admitted with a history of alcoholism had chronic abdominal pain and occasional vomiting but did not reveal anything abnormal on clinical examination. All investigations were essentially negative except that the radiologist reported a filling defect in the intestine. Laparotomy was performed. The surgeon found a few peritoneal adhesions but there was neither obstruction nor any other abnormality. Two months later the patient was still not relieved of his symptoms. The liver was now enlarged, he started getting distension of the abdomen and later a trace of fluid was also suspected. All this time he had occasional rise of temperature and leucocytosis. At first he was put on emetine, later on penicillin and plasma transfusions were given and a second laparotomy was being considered. Before laparotomy a liver biopsy was requisitioned. The biopsy tissue was fatty looking and floated in the formal saline fixative. Histological sections showed a complete fatty metamorphosis of the liver cells. Laparotomy was then abandoned.

INFECTIVE HEPATITIS

The clinical diagnosis of infective hepatitis is usually not difficult. For histological diagnosis the biopsy must be performed early because the characteristic changes are seen only during the early phase of the disease, and no changes may be seen in the liver histology during convalescence. The biopsies in this group of cases were performed in order to study the structural changes in various stages of the disease. The following changes were observed.

Liver cells: There was necrosis of cells diffuse in severe cases but in milder cases it was restricted only to the central zone, midzone or portal zone and occasionally mixed forms were seen. In the diffuse and severe forms, the architecture of the liver might be disorganised but quite often it was surprisingly well preserved. The individual cells showed evidence of necrosis and autolysis resulting in separation of individual cells and loss of pattern. The damaged cells were swollen, sometime the nucleus was also swollen, or there were two nuclei in a cell. Occasionally a nucleus showed mitosis, and with severe damage the nucleus was even absent. The cytoplasm looked granular but in severer cases only deeply stained eosinophilic masses were seen.

Associated with the necrosis there was infiltration of central or periportal regions with mononuclear cells and at times with polymorphonuclear cells as well. In longstanding cases or cases with history of repeated attacks of jaundice fibroblasts may be found in the portal areas and bile ducts may be seen proliferating: subacute nodular cirrhosis.

The sinuses were dilated and the lining cells sometimes show hyperplasia. In many cases where the biopsy was performed late in the course of the disease the liver tissue showed practically no changes.

B. J., male, aged 15, was admitted for oedema of the feet of 6 months duration. There was persistent pain in the abdomen which was unrelated to food. The present trouble started after an attack of jaundice, 7 months before. He had similar attacks of jaundice twice before at intervals of 4 years.

The boy was normally built and fairly nourished. There was slight oedema of the feet. The tongue was pale and smooth, the spleen was +++ firm. Liver was just felt. Urine : N.A.D., R.B.C. 4.04 mill. p. cumm., W.B.C. 5,500 p. cumm. Hb. : 46 per cent. Plasma : protein: total 6.0 6G per cent, a lb. 2.56. glob. 3.5. Stools: N.A.D. Fragility of R.B.C. normal, 0.36 to 0.30. Icterus index 3. Van den Bergh test: negative. Liver biopsy : Liver cells showed fatty degeneration. There was a dense fibrotic area in between a few liver lobules. This showed round cell infiltration and histiocytic proliferation. Bile pigment was seen outside the channels. Diagnosis: Infective hepatitis with fibrosis (Sub-acute nodular type).

Comment: The diagnosis was uncertain in this case and biopsy revealed it. This also shows that repeated attacks of infective hepatitis may ultimately lead to cirrhosis of liver.

KALA AZAR

Biopsy was done in two cases of kala-azar. The biopsy easily showed many Leishman-Donovan bodies whereas a search had to be done in the sternal marrow films for finding the parasites. It is, therefore, felt that this may be an additional method for diagnosis besides sternal and splenic punctures. Further the reticulo-endothelial proliferation and mononuclear infiltrations were very characteristic.

S. M. Male, aged 18 with a past history of malaria was admitted for fever with rigors, cough with expectoration and pain in both hypochondriac regions and back of a duration of 1 year. He was poorly built, ill-nourished. The skin was dry and the nails and mucous membranes were pale. The supratrochlear glands were enlarged. Spleen was enlarged four fingers and the liver 2 fingers and tender. Blood : R. B. C 4.3 mp. cmm. W.B.C. 3,800 p. cmm. polymorph. 64 per cent. All tests for kala-azar were positive. Sternal biopsy : L. D. bodies found. Liver biopsy : under cells bodies present.

AMOEBIC ABSCESS OF THE LIVER

It might be of interest to quote another case in which a male aged 40 had an enlarged, irregular liver which was tender. The patient had temperature upto 99° F. On account of the pain the patient had become an opium addict and used to be always drowsy. The leucocyte count was 8,000 p. cmm. The stools were normal. Screening of the chest did not reveal any abnormality. On account of the marked cachexia and irregularly enlarged liver a tentative diagnosis of malignancy of the liver was made. A request for liver biopsy was made and pus from amoebic abscess was aspirated.

Structural changes in the liver as a result of spirochaetal jaundice and arsephenamine jaundice were also studied by means of liver biopsy. In a case of spirochaetal jaundice biopsy was performed on 4 different occasions.

The following case is cited to show that what was clinically thought to be an enlarged irregular, hard liver turned out to be multiple cysts.

A young girl, aged 13 years, was admitted for swelling of the abdomen of 2 years duration. The swelling started with an attack of pain in abdomen and diarrhoea of one day's duration. The swelling was first noted in the supra-pubic region and gradually increased from below upwards. She was poorly built and ill-nourished. The abdomen was distended, skin was tense, veins were visible and the anteroposterior bulging greater than lateral. On percussion the note was dull all over, there was no shifting dullness. After tapping the abdomen an irregular nodular swelling in the right hypochondrium and epigastrium, moving with respiration and extending six fingers below the costal margin were found. Spleen was not felt. The swelling was taken to be due to malignancy of the liver by several clinicians. There were Rales at both the bases. P. 100 p. min. The heart was pushed up and the apex beat was in 3rd space. Nothing else abnormal. Blood showed anæmia with leucopenia. Plasma proteins total 6 G. per cent. albumin 2.44 G. per cent. globulin 3.56 G per cent. Kahn Test of blood : negative. Icterus index : 4 units, Van den Bergh test;

negative. Urine : normal. Ascitic fluid : rice water colour, clot present, deposit present. Proteins increased. Predominant cells polymorphs ; no organisms. What appeared to be liver was chosen for biopsy but fluid similar to what was believed to be the ascitic fluid was aspirated. No liver cells, no hydatid hooklets. The patient refused to continue her stay in the hospital and the origin and nature of the cysts could not be determined.

CONCLUSIONS

It will be thus seen that liver biopsy has proved useful in.

1. Diagnosis of malignancy of liver in absence of jaundice, cirrhosis of liver and of precirrhotic stage.
2. Finding out whether the liver has been affected in a case of splenic anæmia.
3. Study of structural changes in infective hepatitis, Weil's disease and arsephenamine jaundice.
4. Finding out an amœbic abscess or amœbic hepatitis.

SUMMARY

1. The methods of liver biopsy technique require further assessment before coming into general use.

2. Though the mortality arising from the technique is very small, caution must be exercised in the selection of cases.

3. Selection and preparation of cases for liver biopsy and its technique are detailed; the difficulties and dangers are mentioned. With proper care it is considered as a relatively rapid, reliable and safe procedure.

4. Its value in diagnosis and prevention of unnecessary laparotomies is illustrated by case reports of malignancy, cirrhosis, fatty metamorphosis, etc.

5. It is felt that this procedure is a distinctly helpful addition to our diagnostic armamentarium. With its help one can obtain actual evidence of pathological lesions present at the site of biopsy. Though it does not represent the whole liver, it is often representative enough.

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MEDICAL PROGRESS

NUTRITIONAL MEGALOBLASTIC (MACROCYTIC) ANAEMIA

Y. M. Bhende*

(*Continued from page 166*)

THE AETIOLOGY

Beliefs regarding the ætiology of N.M.A. have passed through phases similar to those in the case of addisonian pernicious anæmia, and, have been moulded, quite naturally, by advances in the knowledge of the latter.

(1) *The Role of Infection in the Aetiology:* In spite of much circumstantial evidence to the contrary, the early workers made repeated fervent attempts to demonstrate the existence of some pathogenic organism in the tissues of the affected individuals, or, to determine, if the normal flora in certain sites had become abnormal in quantity or assumed a pathogenic form. These workers postulated that the bacteria caused, in some manner, excessive destruction of the red blood cells. Balfour[7] cultured the blood of her patients; Wills and Mehta[215] cultured the gastric contents; Balfour[7], Emanuelov and Mehta[57], Wills and Mehta[215], and Mitra[122,123], cultured the urine; Balfour[7], Emanuelov, and Mehta[57], and Gupta[78a] cultured the fæces. No single organism or group of organisms could be constantly isolated, nor could any abnormality be demonstrated in the normal flora in the various sites in the body. Ankylostome infection is not uncommon as a superadded complication. Trowell[184] found that reduction of the worm load and administration of iron did not in many cases cure the anæmia, nor did it reduce the macrocytic element in the anæmia which was amenable to liver therapy. Fairley[61] is of the same opinion. The frequency of positive Kahn test or the Wassermann reaction in patients of N.M.A. has received comment from many workers[7,92,118,145,146,187]. But it is proven that neither syphilis nor malaria, *per se*, can produce the N.M.A. syndrome. The rôle of malaria will be referred to again. Septic complications are not uncommon in N.M.A. patients, especially pregnant females[18]. Though the various infections, by themselves, cannot give rise to N.M.A., it is possible, even highly probable, that they can condition the deficiency

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in patients subsisting on a borderline diet. This is especially true of chronic malaria[138].

(2) *The Role of Toxaemia in the Aetiology :* Presence of some unidentified toxin capable of depressing the erythropoietic tissue in the marrow has been invoked to account for the grave anæmia seen in pregnant females. Balfour[7] thought that the alleged toxin was generated in the products of conception but made a shrewd remark that she had never seen the so-called pernicious anæmia of pregnancy and eclampsia in the same patient. Mitra[122] remarked that the toxæmia of pregnancy manifested itself in several ways—affecting different organs in different cases—and postulated that in pernicious anæmia of pregnancy the toxin affected electively the hæmopoietic system. The degenerative changes seen in the centre of the liver lobules, in his fatal cases, were adduced by him[122] as proof of the toxæmia. Reviewing its then status, an editorial in the *Indian Medical Gazette*[22] pointed out that "tropical anæmia of pregnancy" was a manifestation of toxæmia, from the toxins generated either in the bowel or in the products of conception. Napier and Neal Edward[146] remarked that the association of severe macrocytic anæmia with primigravidity independent of age, its occurrence relatively early in pregnancy, and, its association with premature delivery and a high neonatal death rate suggested comparison with the toxæmia of pregnancy. They did not, however, consider the toxæmia as the sole ætiological factor ; but, this was one factor in the production of a "conditioned deficiency", the other factors being malaria, syphilis, deficient diet, and defective gastro-intestinal function. Napier[138] reiterated these views a little later. Mudaliar and Menon[129], though convinced that the anæmia was in the main a deficiency disease, stated that it behaved like the pre-eclamptic toxæmia of pregnancy. Others have thought that the toxæmia may be due to syphilis or of malarial origin and this thesis was applicable both to pregnant females and non-pregnant females and males. That any kind of toxæmia acting on the hæmopoietic tissue can stimulate a megaloblastic hyperplasia in it is not a plausible hypothesis nor can this concept explain satisfactorily how marmite, liver extracts, and, folic acid could be curative in a condition so produced. Though a case has not been made out for the existence of toxæmia even in the so-called pernicous anæmia of pregnancy, it cannot be denied that from the therapeutic point of view (refractoriness to liver extracts) and from the point of view of the natural history of the disease process (spontaneous remissions) the factor of pregnancy is of some significance in the N.M.A. in pregnant females, and cannot be totally ignored. By no means, however, is that the most important factor.

(3) *The Role of Endocrines:* Callender[18] has reviewed the effects of the administration of the pituitary, androgen and oestrogen hormones on the hæmopoietic system of the experimental animals and pointed out the applicability of such data to man. She believes that the refractoriness of some patients of the pernicious anæmia of pregnancy to liver therapy may be due to the inability of such patients to utilise the hæmopoietic principle as in the case of achrestic anæmia described by Israels and Wilkinson[95,96]. According to her, in pregnant patients, this inhibition may be endocrinal in origin and though the exact nature of the disturbance is unknown she has suggested that œstrin may be the hormone involved.

(4) *The Role of Hæmolysis in the Aetiology:* As in the case of addisonian pernicious anæmia, earlier studies looked upon N.M.A. as a hæmolytic anæmia. Enlargement of the liver and especially the spleen, presence of hyperbilirubinæmia and urobilinuria, and, a high reticulocyte count in some of the cases gave credence to this hypothesis. The search for a hæmolytic agent capable of damaging or lysing the red cell consisted in demonstration of some organism or a bacterial toxin[7,57,78a,122,215], or, a chemial metabolite (like lipoids)[76]. Even the destructive action of the chorionic villi on the mother's red cells has been postulated[118]. Hyperbilirubinæmia, methæmalbuminæmia, spherocytosis with increased fragility of the red cells, a high initial reticulocyte count in an untreated case, and an excessive excretion of urobilinogen in the urine and especially in the fæces may be considered as very sugggestive evidence of a hæmolytic process. Of these, hyperbilirubinæmia and urobilinuria may be produced by a normally fuctioning reticulo-endothelial system destroying the abnormal red cells, like microcytes and poikilocytes, present in large numbers in severe N.M.A. Or, this may mean an excess of pigment over and above that which can be utilised when red cell formation is at fault. Those who have postualted excessive hæmolysis in N.M.A. have based their opinion in the main on the presence of hyperbilirubinæmia, urobilinuria, and, reticulocytosis in the peripheral blood[64,136,138,146,184]. And at the moment the only hæmolytic agent incriminated is chronic malarial infection[72,82,132,137-139,145,163]. It is necessary to reiterate that acute or active malarial infection though detected by many[7,78a,122,159] in their patients is not held of any significance; it is the previous chronic malarial infection that is blamed. It may recalled in this connexion that at the autopsy on fatal cases of N.M.A. the organs show malarial pigment in the reticulo-endothelial cells but no parasites are discovered[64]. It is also interesting to note that in those cases where an active malarial infection was peresent, it did not alter the blood picture[64],

Chronic malarial infection results in a hypertrophied reticulo-endothelial system or what has been called a post-malarial reticulo-endotheliosis[64, 131, 137]. This is brought about in two ways : 1) by the infection *per se* and 2) by the products of hæmolysis due to constant destruction of the red cells by the parasite. "Such reticulo-endothelial system, irritated, activated, and hypertrophied, as result of repeated malarial infection phagocytoses these non-parasitised abnormal corpuscles (megalocytes and megalospherocytes) in considerable numbers with the production of hæmolytic anæmia. The end result is a condition somewhat similar to acquired hæmolytic jaundice "[64]. Note the word "abnormal" ; because, Fairley *et al*[64]. who have put forth this concept imply, that dietetic deficiency plus a chronic malarial infection leading to a hypertrophied avid reticulo-endothelial system, *together*, can bring about a picture of panmyelopathy and megaloblastic hyperplasia in the marrow, thus producing the hæmolytic variant of N.M.A. Mere chronic malarial infection in a patient living on good balanced diet cannot produce the picture[61]. Pure dietetic deficiency alone produces panmyelopathy and megaloblastic hyperplasia of the marrow and thus result in N.M.A. non-hæmolytica[64,136,138]. Wills [210] has now agreed with these views. Napier[131], Napier and Mujumdar[136] apparently attach more importance to the factor of chronic malarial infection ; they believe that excessive hæmolysis produced by the infection may determine deficiency of certain "groups of substances"—probably associated with the vitamin B complex—in an individual on a borderline diet. In other words, chronic malaria with its pathological accompaniments produces a relative deficiency, or, conditions the deficiency, resulting in the hæmolytic form of N.M.A. Napier[136] admits that pure dietetic deficiency alone can produce N.M.A. in a few instances, but, in the majority chronic malaria is an important factor. Granted even this, to describe the anæmia so resulting as "post-malarial hæmolytic anæmia"[160] is open to serious objection. The recognition of this hæmolytic group of N.M.A. brought about by the work of Fairley[61], Napier[131,136], Fairley *et al.*[64] etc., has broadened the original concept of Wills and Mehta[215] and proved that N.M.A. is not a homogeneous group but divisible into two distinct types—the non-hæmolytic and the hæmolytic. The dignostic criteria for the former have been decsribed in detail in the foregoing pages. The diagnosis of the latter, apart from the presence of a megaloblastic anæmia, depends on the clear demonstration of signs of hæmolysis. In a typical case, there will be hyperbilirubinæmia urobilinuria, reticuloctosis and splenomegaly. Of these the last is the least important. A high reticulocyte count if associated with the other signs, singly or in combination, is of greatest significance. There is no information, however, on whether a marrow rendered dyshæmopoietic by nutritional deficiency would show as good a reaction to hæmolysis as a normal marrow. Probably not[61]. Yet a diagnosis of N.M.A. hæmolytica should not be made unless the reticulocytes are fairly high, even in the presence of all the other signs enumerated above. The strict distinction between the two types, apart from the epidemiological and ætiological points of view, is in the main of academic interest. Both respond equally well to specific anti-anæmic therapy[210], and no anti-malarial treatment is neceesary in the hæmolytic group.

(5) *The Role of Nutritional Deficiency : A. The Role of Diet :* Many a worker has analysed the diets consummed by his patients of N.M.A. for a possible clue to the exact factor which is lacking in this anæmia. Long before Wills.and her co-workers[203,211,215,220] proclaimed N.M.A. as deficiency disease some observers[7,174] had commented on the poor quality of the diets taken by their patients. By a general consensus of opinion it is now agreed that N.M.A. is endemic in those parts of the world where poverty, under nutrition and malnutrition are the lot of the majority of the population[128,136,137,156,159,163,168,184,185,187,206,210]. In sporadic cases reported from the better-fed parts of the world the patients have, for some reason or other, subsisted for long periods on poor diets[278]. Even in the so-called pernicious anæmia of pregnancy seen in the western hemisphere the majority of the patients have been poor, living on an inadequate diet[18,44,121,126,199,202]. When the anæmic condition has lasted for some time, distaste for food, discomfort due to glossitis, and, gastro-intestinal disturbances exaggerate the deficiency. The diets of the N.M.A. patients are defective both in quantity (low caloric intake) and quality. The search for the qualitative deficiency was at first concentrated on the vitamin content. Vitamins A C, and D were incriminated in the beginning[104,130,215,220]. Vitamins of the B group were the next suspect and the demonstration of the curative action of marmite focussed all attention on these[64,213,220]. Napier[137], however, came to the conclusion that none of the dietetic surveys made in India had been able to show that the diets taken by the N.M.A. patients were definitely deficient in vitamin B complex. On the other hand in the patients studied by Moore *et al.*[126a] in Birmingham Ala, symptoms of vitamin B deficiency were common ; this was not surprising considering that the authors were dealing specially with patients suffering from pellagra. At the same time, they found that thiamine, niacin, riboflavin, calcium pantothenate, pyridoxine, inositol, p-aminobenzoic acid and choline, given singly or in combination, had no effect on the anæmia of their patients. In recent years, from the vitamins, the emphasis has slowly shifted to the impor-

tance of the proteins in the diet. Wills and Talapade[220], during the dietetic surveys of their patients, had noted the relatively low total and animal protein content of such diets. Subsequently many observers have stressed this deficiency of the proteins[4,11,64,102,126,126a,130,131,137,146,156,163,164,181,182,185,187,198,203,210]. The frequency of N.M.A. among the vegetarians has been pointed out by many[102,130,131,146,162,181,198]. Milk, meat and eggs are a luxury to the majority of the population in this country while social customs and religious beliefs forbid even those who can well afford to eat these products. This explains the frequency of N.M.A. among the middle and rich classes in this country. Hypoproteinæmia is a common finding in N.M.A.[38,39,105,168,171,180,193]. Bethell[11] found an inverse relation between the M.C.V. and the level of the serum albumin in pregnant females. It is interesting to note in passing that diets which are rich in biological proteins—especially animal proteins—are also rich in the vitamin B complex[103]. The importance of proteins in the regeneration of blood has been amply proved by animal experiments[20]. No single amino acid has been claimed as "key" amino acid in haemoglobin synthesis. Smith and Stohlman[164a] have produced a macrocytic anaemia (with megaloblastic marrow) in rats maintained on deaminized casein; they discovered that lysine was the anti-anaemic agent in such rats. Though it has been claimed that the extrinsic factor is a protein derivative[103], no worker has submitted that the proteins themselves may be the extrinsic factor.

5. *B. Deficiency of the Extrinsic Factor :* Wills and her co-workers[104,215,216] realised quite early in their investigations that their patients of N.M.A. were living on an inadequate diet. Wills and Billimoria[211] fed rhesus monkeys diets consummed by their patients and reproduced the N.M.A. syndrome in the animals. These diets were relatively deficient in all vitamins and also in proteins and salts. The addition of large doses of vitamins A and C had no effect on the anæmia but marmite was found to be curative. The clinical trials with marmite in Bombay confirmed the animal experiment results[203,204]. Wills'[203] results with marmite were substantiated by many other workers[72,76a,82,131,132,137,139,145,163]. Strauss and Castle[173,174], incubated marmite with normal gastric juice, and, feeding the mixture to addisonian pernicious anæmia patients found that it produced an adequate hæmopoietic response. The experiment proved that marmite contained the extrinsic factor of Castle and that N.M.A. was due to the deficiency of the extrinsic factor[106]. It was further demonstrated by Strauss and Castle[174] that autoclaving did not destroy the activity of marmite, nor precipitation with 80 per cent alcohol. This suggested that vitamin B_2 or some factor associated with it was the extrinsic factor. It

was argued that the absence of the extrinsic factor in the diet conduced to the development of a megaloblastic anæmia by producing an ultimate deficiency of the anti-anæmic priciple as the anæmia responded to the administration of the crude liver extracts then available. In a series of biological experiments Wills and her co-workers[205,209,214,218,219], Ungley[191] and Lassen and Lassen[111], showed that vitamins B_1, B_4 lactoflavin, nicotinic acid, and vitamin B_6 were not the extrinsic factor. At the same time, similar experiments indicated that, in terms of Castle's hypothesis, the extrinsic factor was present in milk, eggs, brewer's yeast, rice polishings, wheat germ, soya beans, beef, meat, crude casein, peptone and fraction G of liver[17,22,126a,163,178,189,190,224]. Further, it was found, that whatever the extrinsic factor be, it was water soluble[65], thermostable[65], resistant to alkalinization, readily soluble in 70 to 80 per cent alcohol but rapidly destroyed by 90 per cent alcohol, extractable by dilute acetic acid, and, passed through the ultra filter[84]. Some of these properties suggest that it may not be a protein derivative ; on the other hand, it has been argued that if the extrinsic factor is not a protein derivative it is difficult to imagine how it can react with the intrinsic factor which according to the available evidence is a proteolytic enzyme[103]. In search of its identity, Castle *et al.*[22] showed that the extrinsic factor is not thiamin, riboflavin, nicotinic acid, pyridoxine, pantothenic acid, p-aminobenzoic acid, inositol, biotin, xanthopterin or folic acid (pteroylglutamic acid). The claims of the last do not appear to have been settled one way or the other. Cartwright[20], in his review of the dietetic factors concerned in erythropoiesis, remarked "though the extrinsic factor had not been identified, it now seems reasonable that it is related in some way to pteroylglutamic acid". Welch[200], on the other hand, reviewing the present status of pteroylglutamic acid and other hæmopoietic agents, pointed out that folic acid is probably not the extrinsic factor since its distribution in natural materials is differently from that of the extrinsic factor. Heinle *et al.*[86] stated that folic acid and its conjugates were not in themselves the extrinsic factor. Further, folic acid acts orally in the absence of normal gastric juice, and, is effective parenterally as well[9,20,151,168,181,224]. The last argument was answered by Moore *et al.*[125] ; they stated that there was a theoretical objection to this conclusion since there was no information as to the effects of Castle's extrinsic factor injected parenterally. To this day the extrinsic factor has not been isolated in pure form, nor for the matter of that the intrinsic factor, or the anti-anæmic principle[103,210]. The only proof of the existence of the extrinsic factor in certain substances is the biologic test—on incubation with normal gastric juice certain substances are capable of producing an adequate response in patients of addisonian pernicious anæmia, or, that in certian anæmias of dietary origin 80 per cent alcoholic extract of beef muscle produces reticulocytosis and rise in the blood level[126a]. It may be remarked that so long as the extrinsic factor has not been isolated in all purity and its efficacy demonstrated by administering it in pure form to suitable patients, its supreme rôle in the production of N.M.A. cannot be said to have been proven. At the same time it must be conceded that the circumstantial evidence for N.M.A. being due to the deficiency of the extrinsic factor is considerable. Though it has been almost implicitly assumed all round that in N.M.A. the intrinsic factor of the stomach is secreted in normal amounts, actually very few studies have been devoted to support the opinion. Finding that the acid secretion of the stomach was not very much affected in N.M.A. and that the anæmia responded to oral administration of marmite, Wills[203] inferred that in this anæmia, in contrast to addisonian pernicious anæmia, there was no failure of the gastric function. On the same evidence, subequent workers have agreed with this view. Mudaliar and Narsinha Rao[130], finding that they could not confirm the results of Wills[203] regarding the efficacy of marmite in pregnant females suffering from N.M.A. and observing further, that these patients subsequently responded to the administration of liver or stomach extracts, postulated that in this anæmia the deficiency was not of vitamins but of the intrinsic factor. That the response to marmite need not weigh too heavily in favour of a deficiency of the extrinsic factor is indicated by the demonstration that brewer's yeast and marmite when given in large doses will bring about a complete remission in many cases of addisonian pernicious anæmia[9,20,119,151,181,223,224]. The direct evidence on the point at issue is that of Strauss and Castle[175,177] who demonstrated that in pernicious anæmia of pregnancy there is a diminution (temporary) in the amount of secretion of the intrinsic factor. The same is true for the anæmia of sprue[22a]. More recently, Moore *et al.*[126a] found that in N.M.A. of pellagra, in certain cases, the intrinsic factor was completely absent. No studies are available on this point for cases of N.M.A. in this country. It cannot be said from the available evidence that in uncomplicated N.M.A. the presence of the intrinsic factor in normal amounts has been satisfactorily proved. Just, as in the case of the extrinsic factor, again, the circumstantial evidence that this is so, is great.

5. *C. Deficiency of an Independent Hæmopoietic Factor:* In their trials of different liver extracts on the N.M.A. produced in the monkeys by deficient diets, Wills, Clutterbuck and Evans[212,213] discovered that purified liver extracts like Anahæmin and Examen (West and Dakin fraction of liver extract) given parenterally, were inactive, while, a crude liver extract like

Campolon was fully potent. This finding suggested that N.M.A. could not be explained on the basis of a simple lack of the extrinsic factor leading to an ultimate deficiency of the anti-anæmic principle. By treating Campolon and alcohol-soluble acidulated aqueous yeast extract with saturated ammonium sulphate two fractions could be obtained from each, one soluble and the other insoluble in saturated ammonium sulphate solution. The insoluble fraction from Campolon (containing any Anahæmin, if present) given parenterally , induced remission in addisonian pernicious anæmia patients, but, not in the anæmia of the monkey. The soluble fraction, on the other hand, given subsequently to the monkey was active. Similarly, the insoluble fraction of the yeast extract, when given orally, was inactive in the monkey but the soluble fraction was quite potent. The possible absence of accessory factors such as those described by Jacobson and Subbarow[98] was ruled out. The experiments led the authors to conclude that both the factors—the soluble and the insoluble fractions—were necessary for hæmopoiesis in man and the rhesus monkey, but, that in the production and cure of the N.M.A. of the monkey, it was the soluble fraction that was mainly concerned; and further, that the two hæmopoietic factors were present in such substances as liver, autolysed yeast and wheat germ. They could say nothing of the exact nature of these factors except that they (the factors) could be part of the vitamin B complex. Napier[131], adopting Greenspon's[77] interpretation of Castle's experiments regarding the extrinsic and the intrinsic factors, pointed out that N.M.A., as seen in India, was due to the deficiency of an independent hæmopoietic factor present in crude liver extract and marmite. "The deficiency of this substance may be absolute or relative, or, it may be due to failure of absorption in the intestinal tract of the substance itself, or, the substance into which it is converted." The evidence for this independent hæmopoietic factor was produced a little later when Napier[134] confirmed the animal experiment results of Wills, Cluttebuck and Evans[212],[213] by demonstrating the inefficacy of Anahæmin in human N.M.A., Wills and Evans[214], working in Bombay, confirmed this; they treated 7 cases of N.M.A. with Anahæmin in doses prescribed for addisonian pernicious anæmia in relapse, but, there was no satisfactory response, though, when crude liver extract was given subsequently these cases did react. It may be noted that, here again, the response was not comparable with that obtained with crude liver extract in addisonian pernicious anæmia. Napier[136],[144], however, showed subsequently that in some cases at least a cure was effected in N.M.A. by massive doses of Anahæmin in conjunction with a good hospital diet. With moderate dosage the response was irregular and unpredictable. Foy and Kondi[66] had the same experience in Macedonia. The ineffectiveness of the purified liver extracts in doses effective in addisonian pernicious anæmia was observed by many workers both in the tropics and in temperate climates[44,70,121,130,154,180,191]. Emphasising the complexity of the problem Napier[136] stated: "one finds, in clinically and hæmatologically identical cases classical, response to Anahæmin in one, late response in another, no response in a third, and, on the other hand, a non-hæmolytic case with no splenic enlargement responding in exactly the same way as a hæmolytic case with a large spleen". Comparing the response of N.M.A. and addisonian pernicious anæmia to marmite, Anahæmin, Campolon, and, other crude liver extracts, Napier[136] concluded that the extrinsic factor could not be identified with the food factor of N.M.A. and the suggestion that the food deficiency in N.M.A. was the deficiency of an independent substance, or, a group of substances had to be seriously considered. Reviewing the status of N.M.A. in pregnant upto 1941, Napier[137] opined that though the actual identity of the substance responsible for Wills' macrocytic anæmia had not been disclosed, a large number of substances formerly proposed had been excluded, including Castle's extrinsic factor. It will be seen that the concept of an independent hæmopoietic factor was based almost entirely on the response of the N.M.A. patients to the so-called purified and crude liver extracts; further support was lent to this thesis by the observations that, in some cases of N.M.A., where both refined and crude liver extracts proved unsatisfactory oral liver extract administration or autolysed yeast by mouth succeeded[9,20,121,151,168,181,224]. Later reports on the potency of refined liver extracts were much more favourable than the original. Foy and Kondi[66] and Fairley[63] observed this in Macedonia and Moore *et al.* [126a] in U.SA.; and these workers cautiously suggested that perhaps N.M.A. as met with in these places, differed in certain respects from its counterpart in India. Moore *et al.* [126a] were even more cautious and added that the purified liver extracts used by them might have contained some hypothetical substance not present in Anahæmin. That no such assumptions were necessary was indicated by the newer data collected in India. Mudaliar and Menon[130] reported that in their hands both crude and purified liver extracts proved equally effective in N.M.A. of pregnant females. Sunderam[180] treated 15 cases of N.M.A. with purified liver extracts (Anahæmin, Examen, Reticulogen) in doses of 2 ml. on alternate days for ten doses; the majority showed a gratifying response and in 2 cases which did not react septic or infestative inhibiting factors were the culprits. He concluded that no case had been made for an independent hæmopoietic factor whose absence caused N.M.A. Patel's[154] experience was similar; in addition, he showed that purified liver extract was effective even in smaller dosage than employed by Sunderam[180]. The case for an independent hæmopoietic factor was re-opened by Ahmed[1]. Five cases of macrocytic anæmia were found refractory to purified and crude liver extracts parenterally, marmite, and, high protein diet; subsequent treatment with whole liver, yeast, or nicotinic acid produced the desired response. The author argued that the so-called independent hæmopoietic factor was none else than nicotinic acid, and, that the deficiency of nicotinic acid acted either by interfering with the secretion of the intrinsic factor or preventing its combination with the extrinsic factor, in either case making the anæmia refractory to ordinary therapy. The data on which the theory was built up is too meagre and no good case can be said to have been made. Davis and Davidson[51] found that proteolysed liver (papain digest of whole liver for oral administration) was superior to fractionated liver extracts given parenterally in certain cases of refractory megaloblastic anæmia, and, seeking an explanation for this superiority, they believed that proteolysed extract contained some factor of hæmopoietic value lacking or present in inadequate quantities in fractionated liver extract. They put forth a provisional hypothesis that while in the great majority of the cases megaloblastic anæmias were due to deficiency of Castle's anti-anæmic principle, in refractory megaloblastic anæmias the maturation of megaloblasts failed because of the absence of an additional factor from its failure of production or absorption ; the efficacy of this unknown factor was contingent upon an adequate quantity of Castle's antianæmic principle being made available. It would be attractive to apply this hypothesis of Davis and Davidson[51] to the situation present in some cases of N.M.A. Das Gupta *et al.*[39] treated 15 cases of N.M.A. with proteolysed liver extract ; an extract, derived from 100 grams of raw liver, given for 10 to 20 days, was sufficient to bring the blood picture to normal in all cases with frankly megaloblastic marrow. Patients with dimorphic erythropoiesis required bigger doses and longer treatment. However, no details of the marrow picture were supplied in the paper and the authors did not attempt to establish the superiority of proteolysed liver over the usual purified or crude liver extracts. In a further report Das Gupta and Chatterjee[38] recorded that in 1 case of N.M.A. folic acid therapy caused much clinical and hæmatological improvement but without the blood being restored to the normal level or the M.C.V. returned to within the normal range. Subsequent administration of proteolysed liver produced an added hæmatological response and the M.C.V. was brought to the normal level. These findings lend support to the contention of Davis and Davidson[51] that proteolysed liver contains some additional factor. The same paper of Das Gupta *et al.*[38] illustrated that out of 7 cases of N.M.A. treated by folic acid 6 showed a good response. In none of them, however, was the M.C.V. restored to its normal value. Further treatment with ordinary liver extracts produced another hæmatological response and the M.C.V. was brought within the normal range. The authors postulated that the deficiency in N.M.A. could not be fully made up by folic acid alone, and, that probably two factors were necessary to bring about a complete remission in N.M.A.: one of the factors, the stimulating factor, was responsible for mere accelerated formation of new red cells and the other factor, the maturation factor, was necessary for the proper maturation of the red cell. Liver contained both these factors in equal proportion, marmite and good diet likewise both but in small amounts with the maturation factor preponderating, folic acid both the factors again but the stimulating factor preponderating. The authors did not discuss the nature of these factors. Watson and Castle,[199] studying the effects of purified liver extracts given parenterally, crude liver extracts given parenterally, and, liver extracts administered orally, came to the conclusion, that at least two, and possibly three types of nutritional deficiencies exist in N.M.A. : (1) corrected by the usual amounts of most refined liver extracts given parenterally, (2) corrected by oral administration of crude liver extract or, by large amounts of crude liver extracts given parenterally, (3) corrected by crude liver extracts or autolysed yeast, given orally. According to these authors, the independent hæmopoietic principle present in crude liver extracts and autolysed yeast should be called "Wills' factor". Such a possibility of more than one factor being deficient in N.M.A., if established, may suggest the further possibility that the same factor may not be lacking in different cases of N.M.A., encountered in any country, or, at least, in different countries. The study of cases of the so-called pernicious anæmia of pregnancy in the West, from this new angle, is also warranted and the new data collected in this manner may wipe off the difference that some authorities believe to exist between the megaloblastic anæmia of pregnancy in the tropics and that of the West or temperate climates. In a very pertinent discussion on the nature of the injected liver extracts, Emery and Hurran[58] pointed out that when the manufacturing process of the purified liver extracts was so modified as to avoid any losses during fractionation and the efficacy of the extract expressed in terms of the original mass of the liver from which it was derived, there was no discrepancy between the crude and the refined liver extracts so far as a satisfactory response in addisonian pernicious anæmia was concerned. According to the authors, the degree of the purification of the different liver extracts could be best expressed by calculating the purification index, provided the potency of the extract was indicated in terms of an arbitrary unit and the content of the solids in the extract was known. They remarked : "Consideration on a unitage basis of dosage requirements in the treatment of the more complex macrocytic anæmias (like N.M.A.) *might lead to a resolution of the divergent* views which are at present held in the relative efficacy of crude and refined extracts". Wilkinson and Israels[221] have uttered a similar warning. Upto date no such studies have been reported. Wills,[210] in a very recent review, came to the conclusion that endemic N.M.A. is an unconditioned deficiency, the deficiency being of a factor other than the liver principle, possibly a co-enzyme present in association with good biologic protein and vitamin B complex.

5. *D. The Animal Experiments:* McCarrison,[116] as early as 1927, had produced in rats a fatal anæmia, "resembling addisonian pernicious anæmia" by feeding them on a diet composed of oat meal, cornflour, linseed meal, and a mixture of sodium chloride, calcium and phosporus. Wills and Mehta[215] examined the available blood films from such animals and agreed that the blood picture resembled that of their patients of N.M.A. The marrow changes were presumably not studied. The anæmia was attributed to deficiency of vitamin A plus the toxic action of the linseed on the urinary tract. Koesler *et al.*[104] similarly claimed, that they had reproduced addisonian pernicious anæmia in rats by keeping them on a diet deficient in vitamin A. Wills and Mehta,[217] basing their experiments on McCarrison's[116] earlier work, fed rats on (1) diets consumed by their patients of N.M.A., (2) synthetic diets of various kinds; their results indicated that by dietetic means alone a Bartonella anæmia could be reproduced in the animals. They attributed the anæmia to deficiency of vitamins A and C; no evidence was put forth to exclude a spontaneous infection. Later, Wills and her co-workers[211, 214, 219] fed rhesus monkeys on diets taken by their N.M.A. patients (polished rice, margarine, white bread, cod liver oil, and either tomatoes or carrots) and produced a macrocytic anæmia; "the anæmia resembled that of T.M.A. and the marrow picture was that of megaloblastic type". Vitamins A and C were ineffective in curing the anæmia but marmite was curative and so was Campolon. Strangely enough Anahæmin was found impotent. These findings led the authors to postulate the deficiency of an independent hæmopoietic factor as the underlying basis for N.M.A., and abandon the earlier view of the extrinsic factor being the missing factor. The properties of this new factor were never defined in positive terms; nicotinic acid, pyridoxine, riboflavin, pantothenic acid, p-aminoben-

zoic acid were excluded, though, a mercuric acetate precipitate prepared from marmite and Campolon was shown to contain the curative factor[209]. Whatever the unindentified substance was, in all known properties it resembled Castle's extrinsic factor[20]. Napier[137], however, failed to confirm the production of N.M.A. in the monkey by Wills' methods ; he was able to show that the recovery time in monkeys subjected to repeated bleedings was much longer if the animals were kept on a diet deficient in vitamin B complex than when they were reared on a well balanced diet. The relationship of this anæmia produced in the monkey by Wills[211-214, 219] and that produced by Day and his co-workers[52, 52a, 110a] and attributed to vitamin M deficiency is not clear. It is interesting to recall that in the latter, the anæmia was normocytic and was accompanied by leucopenia and thrombocytopenia[20]. Darby and Jones[36] have suggested that vitamin M deficiency in the monkey may be considered the experimental analogue of sprue in man (although be it noted that purified liver extract has no effect on the vitamin M deficient monkey). If the contention be admitted, vitamin M deficiency is brought very much closer to N.M.A. In fact Wills[210] recently suggested that the relationship of folic acid to the vitamin M deficiency in the monkey lends support to the view that possibly folic acid may be the missing factor in N.M.A. The clinical experience with folic acid does not support this[38]. Rhodes and Miller[156a] by feeding swines with a modification of the diet that produces black tongue in dogs, could produce in these animals changes—hæmatologic, lingual and gastro-intestinal—similar to those of addisonian pernicious anæmia. Cartwright[20], however, has pointed out that the anæmia was not macrocytic. Cartwright, Wintrobe and Humphreys[21] fed a single young pig on a basal diet containing pure casein (supposedly lacking in the extrinsic factor) to which 2 per cent. sulfasuxidine was added. The animal ceased to grow normally and developed alopecia and a normocytic and slightly hypochromic anæmia. Four animals maintained on a similar diet but with crude casein substituted for purified casein and to which sulfasuxidine was added did not develop any anæmia. Treatment with highly purified anti-pernicious anæmia extract restored the growth and the blood picture became normal. The authors cautiously added " whether the anæmia occurring in this animal was the counterpart of pernicious anæmia in human beings we are unable to state." Heinle Welch, George, Epstein and Pritchard[86] produced a macrocytic anæmia in pigs by administration of folic acid deficient diet and with added crude folic acid antagonist. The marrow was megaloblastic and the gastric juice contained free hydrochloric acid. The anæmia improved with extrinsic factor alone—addition of normal human gastric juice was shown to be unnecesssary. Purified liver extract as well as folic acid (intramuscularly) were equally effective. It would appear that Cartwright *et al.*[21] and Heinle *et al.*[86] have very nearly approached the successful reproduction of the human condition (N.M.A.) in the experimental animal. The animal experiments cannot be said to have solved the problems of the ætiology and the pathogenesis of N.M.A. but they have placed a valuable tool in the hands of the experimental physiologist for further progress in the knowledge of the subject.

RELATIONSHIP TO MEGALOBLASTIC ANAEMIA IN OTHER DISEASES

The exact relationship of uncomplicated N.M.A. to nutritional macrocytic anaemia seen in pallegra and sprue is not defined. Some clinical features, laboratory data and aetiological factors are common to all the three.[60] Wills[210] has critically reviewed the inter-relationship between N.M.A. and tropical sprue and put forth the tentative conclusion that though both N.M.A. and spure have the common characteristic of the presence of a panhaemopoietic dystrophy characterised by a megaloblastic erythropoisis, the two are distinct entities, with essentially different natural histories, pathological pictures and aetiological basis, and, therefore, should be separated from each other. Fairley[60] and Napier[138] are of the same opinion and point out that in all cases of sprue a megaloblastic anœmia is not a constant accompaniment. Same was the experience of Karamchandani and Ghulam Hyder[101]. Though, uncomplicated N.M.A. and pellagra are even closer to each other than N.M.A. and sprue, in the present state of our knowledge the same above conclusions would apply to the relationship between them: not all cases of pellagra show a megaloblastic anæmia.[135, 202, 203, 224]. The idiopathic refractory megaloblastic anæmias[43, 51] and the achrestic anaemia of Israels and Wilkinson[95, 96] have to be reassesed aetiologically in the light of the new weapons like proteolysed liver and the folic acid compounds before their exact statuscan be defined; direct dietary deficiency is probably not an aetiological factor in these types, though alimentary dysfunction with defects of absorption may be concerned.[43] Refractory megaloblastic anæmia does not respond to parenteral administration of purified liver extracts even in massive doses but, reacts to oral liver, proteolysed liver and folic acid;[43, 51] this behaviour brings it nearer to N.M.A.

DIFFERENTIATION OF N.M.A. FROM ADDISONIAN PERNICIOUS ANAEMIA

N.M.A. is a very common condition in this country while addisonian pernicious anæmia is rare but not unknown. The latter is mainly a disease of temperate zones[202, 224] and the geographical distribution of the two is therefore different[210]. Addisonian pernicious anæmia has proclivity for certain races, though it is not exclusively confined to them[224]. Within these racial groups both the sexes and all social strata are affected. Genetic and constitutional factors play an important role and familial incidence is a feature. In all these respects N.M.A. is entirely different. A history of subsistance on a poor diet is always obtainable in N. M. A. The peculiar age incidence, absence of any emaciation and the occurrence of natural remissions are common attributes of addisonian pernicious anæmia. A natural remission in N.M.A. occurs only after delivery when the anæmia is encountered in a pregnant female[212]. Of the physical signs, except for one single exception,[53] subacute combined degeneration of the cord has never been recorded in N.M.A. Though a few differences have been emphasized in many reports, in general, haematologically, N.M.A. is indistinguishable from addisonian pernicious anæmia[168,202,224]. In fact a typical blood picture of addissionian pornicious anæmia without the associated symptom complexes—lemon yellow discolouration of the skin, atrophic glossitis and neurological disturbances—is, many times a feature of N.M.A.[203]. Microcytosis or normocytosis with a megaloblastic marrow has so far not been described for addisonian pernicious anæmia. In N.M.A. haemoglobinised megaloblasts are rarely seen in either the peripheral blood or the marrow; they are never plentiful in either location. Since urobilinuria and bilirubinaemia can occur in N.M.A. of the haemolytic type, the original contention of some observers,[136,212,215] that the presence of haemolysis in addisonian pernicious anæmia and its absence in N.M.A. in a fundamental distinction between the two, has to be modified. Wills[210] has already accepted this modification. Some have emphasized the high serum iron values in addisonian pernicious anaemia[95]. A permanant histamine—fast achlorhydria is a characteristic finding in addisonian pernicious anæmia; majority of the cases of N.M.A. show free hydrochloric acid in the gastric juice. In a few that do show a histamine—fast achlorhydria the acid may return after treatment.[42,117,181]. The intrinsic factor in the gastric juice is absent in addisonian pernicous anæmia; in N.M.A. it is presumed to be present in normal amount. Related to this is the absence of any non-inflammatory atrophy of the gastric mucosa in the latter.[156] The difference in the morbid anatomy of the two disease processes has been fully discussed by Wills.[210] Aetologically, addisonian pernicous anæmia is conditioned deficiency—a permanent one—due to a defective gastric mucosa failing to produce the intrinsic factor; N.M.A., in its uncomplicated form, at least, according to most, is a direct (unconditioned) deficiency, exogenous in origin, at times precipitated or exaggerated by latent chronic malaria, pregnancy, and, lactation.[210] The exact pathogenosis of the two is at the moment not understood, but, on *a priori* grounds, would appear to be not the same. One fact is however firmly established, that in N.M.A., in contrast to addisonian pernicous anæmia, genetic factors are of no significance. From the point of view of the treatment the two are in marked contrast to each other; in addisonian pernicious anæmia life-long maintenance therapy has to be continued for fear of haematologic or neurologic relapses;[202,224] in N.M.A. once the blood has been restored to its normal value good diet alone will keep the individual fit. The last point stresses the importance of establishing correct diagnosis right at the outset.

PATHOGENESIS

All the evidence available—ethnic, epidemiological, clinical, therapeutic, and experimental—suggests that N.M.A. is of nutritional origin and is a deficiency disease. The exact factor(s) that is lacking has not been spotted, but, it is certain that the deficiency is exogenous in origin —the missing factor is present in the diet of the normal individual but is absent in the diet of the patient suffering from N.M.A. As a consequence of the classic investigations of Castle and his associates, most studies bearing on the ætiology of the macrocytic anæmias have been concerned with attempts to relate the condition under consideration to the deficiency of a gastric (intrinsic) or dietetic (extrnsic) factor, to some disturbance of their interaction, or, of the absorption or utilization of the products of interaction of these factors. On this attractive hypothesis, N.M.A. was defined as due to absence of the extrinsic factor in the diet, and, addisonian pernicious anæmia as due to the failure of the production of the intrinsic factor by the gastric mucosa[202,224]. Therapeutic observations showed that this " unitarian " hypothesis concerning the ætiology of addisonian pernicious anæmia could not be applied uniformly to all cases of N.M.A. and some workers conceived of an independent hæmopoietic factor as the missing element in N.M.A., either Wills' factor as Watson and Castle[199] have called it or an unidentified unnamed factor[70,136,137,213]. It is not improbable that this factor may not be a single element; many different factors—" groups of substances "[136]— may be concerned, and, N.M.A. in different parts of the world may be due to deficiency of different substance(s) each peculiar to its own endemic region. The deficiency of this substance(s) may be simple and direct— due to its long continued absence in the diet[64,83,115,164,198,199,210], or, on the other hand, the deficiency may be conditioned[136,137,138,194], because of the increased need for the substance(s), as in pregnancy and lactation, or, in latent chronic malaria[136,137,138,146]. The recent discovery of the effectiveness of simple substances like folic acid and the allied products[47,110,168], thymine[68,69,170] and pterins[149], in addisonian pernicious anæmia and nutritional anæmias, has taught us that a reorientation of the views regarding the mode of action of the hæmopoietic substances and the underlying basis for the disturbed hæmopoiesis is necessary. Emphasis has shifted from a mere presence or absence of a maturation factor to fundamental and widespread alteration in cellular metabolism. For instance, evidence is at hand to show that pteroylglutamic acid (folic acid) plays an essential rôle in metabolism in man[200]. It has been argued that the various anti-anæmic factors correct this disturbed cellular metabolism ; they may act in a similar all-over manner but by different routes[10,200]. It has been further postulated, that the megaloblastic anæmias result from dyshæmopoiesis brought about by a breakdown of some intracellular enzyme system in which the anti-anæmic principle plays an important part[150,151,210]. The exact nature of the anti-anæmic principles is as yet unknown ; folic acid is not the anti-anæmic principle[10,150,200,210]. It has been suggested that pteroylglutamic acid exists in natural sources mostly in combined forms, as conjugates, (pteroylglutamates) which cannot be utilised by the body unless broken down and the contained pteroylglutamic acid liberated in free form. The spontaneous breaking down of the conjugates in the body is inhibited by the conjugase-inhibitors, present naturally in some of the conjugates, and, in animal tissues[151,152]. A normal person can break down these conjugates by enzyme action (conjugase-action) ; some patients of addisonian pernicious anæmia cannot[150,151,201]. However if such patients are given liver extract they are enabled to do that, as shown by the increased excretion of free pteroylglutamic acid in the urine[150]. The plausible hypothesis put forward is that one of the biochemical defects resulting from the deficiency of the anti-anæmic principle in addisonian pernicious anæmia consists in this abnormality in the derivation of free pteroylglutamic acid from its conjugates[151], because of the partial or complete failure to inactivate the conjugase-inhabitors[179]. This has not been proved[200] ; animal experiments do not support this assumption[86]. It has also been suggested by Swenserd[180a] that the function of normal gastric juice is to destroy the inhibitors, and, in addisonian pernicious anæmia, this mechanism fails. Again, this assumption has not so far been put to test and proved. On the other hand, in N.M.A. and sprue, both the free folic acid and a conjugate—pteroyltriglutamate—have been shown to be effective[73,100,179]. Davidson and Girdhood[48] have pointed out that deficiency of folic acid may arise from (i) failure in the intake of conjugated folic acid as in N.M.A., (this is disproved by Heinle and Welch[85]), (ii) failure of absorption of conjugated folic acid as in sprue syndrome, or (iii) failure of liberation of free folic acid from its conjugates as in addisonian pernicious anæmia (this does not hold for all patients[200]). The failure of potent purified liver extracts in N.M.A., sprue, and, the so-called pernicious anæmia of pregnancy is explained by the deficiency in the body of conjugated folic acid as a result of direct deficiency or a failure of absorption. On the other hand, Welch[200] reviewing the present position of pteroylglutamic acid and other haemopoietic substances put forth the following hypothesis : "For the formation of erythrocytes leucocytes, and doubtless of other types of cells, many compounds must be formed. For the synthesis of some of these, let us suppose that the anti-pernicious anaemia factor is utilised catalytically presumably in the form of one or more enzymes. But, let us suppose also that in man another pathway of synthesis of some of those compounds and probably other compounds as well is catalysed by pteroylgutamic acid. Thus the human subject might be supposed to derive material suitable for the formation of new erythrocytes by virtue of either type of catalysis, because of the overlapping in the synthetic accomplishments of the two factors. Very likely, however, neither factor can be fully dispensed with and the state of pernicious anaemia would reflect deficiency of both substances." Heinle *et al.*[86] opinied that the data available fail to support this thesis. The occurrence of neurologic relapses in patients of addisonian pernicious anaemia maintained on folic acid[196] and the fact that in the different animal species liver extract and folic acid cannot replace each other are cited as evidence for this hypothesis. To anyone who cares to persue the available literature on the mode of action of folic acid and the allied compounds, it would seem that no dogmatic statements are pertinent at the moment. This must await full knowledge of what Welch[200] would call "the biochemistry of the synthesis of new cells." All that can be said is that addisonian pernicious anæmia and the related anæmia arise from a disturbed biochemistry of the erythron. The normal functioning of the erythron depends on the presence of certain substrates, enzymes and coenzymes, inhibitors and activators, and, inbalance of these results in disturbed haemopoiesis.

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EVALUATION OF RECTAL SYMPTOMS

A. E. de Sa *

The two extremities of the alimentary tract, the mouth at one end and the rectum and anus at the other, present special problems both to the patient and the physician.

Nature appears to have conspired with tradition to make the former accessible and open, the latter hidden away in the natal cleft and invested with secrecy. This may account for the reluctance of so many physicians to do so much as a digital examination of the rectum in patients whose symptoms demand such a measure. Consequently, many symptoms that could be explained by an examination of the rectum and anal canal are passed off with a placebo. Only too often has carcinoma of the rectum been permitted to advance to a stage of inoperability, treated as a case of dysentery with emetine and other amoebicides when a straight digital examination would have revealed the true condition. It has been said with profound irony "If you do not put your finger in you will put your foot in it." Whereas opening the mouth and examination of the fauces are the stock in trade of the most casual physician, rectal examination seems for some reason to have been taboo.

The purpose of this article is to evaluate the significance of rectal symptoms and to stress the importance of basic examinations in arriving at a correct diagnosis.

Ano-rectal diseases manifest themselves with one or more of the symptoms listed below, though it must always be borne in mind that the early stages of rectal disease are often remarkably free from symptoms.

The usual presenting symptoms in rectal disease are:—

1. Hæmorrhage.
2. Pain.
3. Prolapse.
4. Pruritus.
5. Discharge of pus and mucus.
6. Diarrhoea.
7. Incontinence.
8. Tenesmus.

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HAEMORRHAGE

Internal haemorrhoids are the commonest cause of bleeding per rectum. The haemorrhage may vary from a few drops to a few ounces at a time. The blood may ooze out in drops or spurt out in a jet, following the passage of a stool. In later stages bleeding may occur apart from defæcation. It is worthy of note that bleeding may occur internally as well, and the ampulla of the rectum may be ballooned with blood before any external bleeding is seen. The bleeding may be prolonged enough or severe enough to produce a marked anæmia.

Anal fissure may cause streaking of the stool with blood, but pain is the symptom that overshadows the bleeding.

Rectal Neoplasms notably polypi in children, are a frequent cause of rectal hæmorrhage in the early years of life. The diagnosis of a pedunculated polyp is easily made by a digital examination. Careful proctoscopy reveals a cherry-like swelling which hangs by a stalk; but it is not unusual for the polyp to be masked by folds of rectal mucosa.

Neoplasms causing rectal hæmorrhage in adults are either benign or malignant. The benign tumour may be a solitary adenoma or part of a generalised colonic adenomatosis, or a villous papilloma. Multiple adenomata as well as villous papilloma are precancerous conditions.

Of the malignant lesions of the rectum, carcinoma is the common cause of rectal hæmorrhage.

Intussusception as a cause of rectal bleeding is second only to a rectal polypus in the early years of life. The associated symptoms of the condition are diagnostic enough—periodic attacks of colicky pain in an otherwise healthy child, the presence of a sausage shaped abdominal lump and the characteristic stools which consist of little fæcal matter with plenty of bloody mucus. Rarely a bloody discharge per rectum and the presence of a sausage shaped lump in the abdomen are the only manifestations of the condition. In the rare case where the intussusception presents at the anus there should be no difficulty in distinguishing the condition from prolapse or a polyp. Whereas the reflection of the mucosa on to the rectal wall can always be made out by digital examination of a rectal prolapse, intussusception presents no such reflection. A prolapsing polyp always hangs by a stalk and lacks a central lumen.

Meckel's diverticulum with peptic ulceration is an occasional cause of rectal hæmorrhage.

PAIN

Though pain is an obtrusive rectal symptom from the patient's point of view it rarely indicates a grave rectal lesion. The rectum above Hilton's line is insensitive to painful stimuli, and hence advanced rectal cancers may be free from pain till such time as they invade the anal canal or spread into the perirectal tissues. Painful ano-rectal conditions may be classified in the order of their frequency as:—

Anal fissure. This is really an ulcer occurring in the posterior anal wall and is easily demonstrable in the most recalcitrant patient by a firm but gentle separation of the buttocks. A small hypertrophic skin tag marks the lower end of the fissure. Pain in anal fissure is characterised by its severity and appearance immediately after defæcation. In rare cases the pain may radiate down the backs of the thighs and be severe enough to cause retention of urine.

Peri-anal suppuration. Peri-anal and ischio-rectal abscesses fill this section. The presence of an inflammatory swelling near the anus together with the history of throbbing pain in that region is diagnostic.

Acute anal haematoma or thrombotic external pile is an extremely painful condition characterised by the appearance of a cherry-like swelling at the anal verge. The history usually obtained is that of great straining at stools followed by the appearance of the swelling which is caused by the rupture of the superficial peri-anal veins.

Strangulation of internal prolapsed piles is a painful condition characterised by the presence of a bluish mass projecting from the anus. The mucous membrane on the surface is usually ulcerated and the diagnosis does not present any difficulty.

Rectal neuralgia and cauda equina tumours are occasional causes of rectal pain. The absence of any objective physical signs in the former and the signs of a space occupying spinal lesion in the latter should suggest the diagnosis. The pain of rectal neuralgia is intermittent and aggravated by psychic storms.

PRURITUS

Pruritus is a common enough symptom and though there is a group of cases which is primary and based on a psychosis, the majority are traceable to some local cause. Among the local causes are:—

Thread worms: These may migrate outside the anus and cause severe pruritus especially at night. The diagnosis presents no special difficulties as the worms are often seen wriggling about the anus. If not visible on external examination or proctoscopy, routine stool examination will reveal the ova of the worms.

Increased anal moisture such as results from the hypertrophied rectal mucosa that obtains in haemorrhoids or rectal prolapse. The primary cause is usually apparent. Lack of local cleanliness and increased anal moisture due to hypertrophied anal papillae are other causes of pruritus.

Occupational pruritus occurs in stokers and engine drivers due to excessive sweating.

Diabetes mellitus—a rare cause of pruritus ani is diagnosed by a routine urinalysis in the apparently causeless case.

Primary or psychogenic pruritus is diagnosed by a process of elimination. A vicious circle is easily started.

Skin infection : ↗ severe irritation ↘ loss of sleep.
↖ scratching ↙

DISCHARGE OF PUS OR MUCUS

Purulent discharge from the rectum may occur in extensive fistulae-in-ano where there are multiple openings into the rectum and anal canal, though in the large majority of cases the discharge is only external, on to the peri-anal skin.

The bursting of a pelvic abscess into the rectum would be signalised by a profuse discharge of pus per rectum. Other signs of intra pelvic suppuration and perhaps the characteristic *B. coli* smell would help to establish the diagnosis.

Lymphogranuloma of the rectum is often characterised by the passage of large quantities of muco-pus per rectum.

The passage of pure mucus unmixed with pus is not a common rectal symptom though it has been noticed in round worm infestation in children. Dysenteric colitis with proctitis is a common cause, another being mucus colitis, which fortunately is rare in our country.

Villous papilloma of the rectum is often characterised by the passage of mucus streaked with blood.

DIARRHOEA

Diarrhoea as a symptom of rectal disease is often the other face of constipation. In other words the very conditions that causes the obstruction are responsible for the production of diarrhoea. Among such conditions are granulomatous and neoplastic strictures of the rectum, villous papilloma of the rectum and ulcerative proctitis from any cause.

The sudden onset of diarrhoea alternating with constipation or any sudden change of bowel habits in an individual over 50 years of age will give the shrewd clinician a clue to the probable onset of malignancy.

CONSTIPATION

Constipation is not a common symptom of rectal disease. It may be secondary to anal fissure. The excruciating pain on defaēcation effectively inhibits the passage of a stool ; consequently, the hard scybalae set up a vicious circle of pain—fear—constipation—pain.

TENESMUS

True tenesmus is found in those conditions where there is marked irritation of the rectum and lower colon. Ulcerative proctitis, amoebic and bacillary dysentery are other causes.

INCONTINENCE

Incontinence is a rare symptom of rectal disease except in the very old where there is laxity of the anal sphincter as the causative factor. Incontinence may result from injudicious surgery following high section of the anal sphincter in the region of the ano-rectal ring in an operation for fistula-in-ano, or over-dilatation of the sphincter at operation.

The incontinence that occurs in such medical conditions as tabes dorsalis and disseminated sclerosis must be borne in mind but it will hardly ever be the dominant feature of these conditions.

Spinal tumour and spinal trauma are also to be thought of. Though the symptoms enumerated above appear to make a formidable list, the diagnosis of rectal conditions should present no problem to the general practitioner, so long as he is alive to the importance of basic examinations.

CURRENT MEDICAL LITERATURE

MEDICINE

ORAL EMETINE IN THE TREATMENT OF INTESTINAL AMOEBIASIS. Bliss C. Sharpneil. Am. Jr. Trop. Med. **27**: 527-544, 1947.

The paper begins by referring to the same author in Am. Jr. Trop. Med. 26: May 1946. pp. 293-310, which is a preliminary report on trials of emetine hydrochloride orally in the treatment of intestinal amoebiasis. The present paper gives a table showing amoebicidal activity of chiniofon, carbarsone, vioform, and emetine hydrochloride as investigated by Kessel (1928), Leake (1932), Leake (1932), Dobell, Laidlaw, and Bishop (1928), and St. John (1932), respectively, the last two dealing with emetine hydrochloride. A set of 30 cases treated with enteric coated tablets of emetine hydrochloride, age group ranging from 17 months to 66 years, included 8 acute, 15 chronic, and 77 carriers. All were hospital cases. There was no attempt at selection but cases that had emetine hydrochloride subcutaneously and cases that did not show E. histolytica were not included.

The standard dosage schedule followed was as follows:—

Children—1 tablet (½ grain) of emetine hydrochloride orally three times a day for 12 days: 12 grains in 12 days. Adults—2 tablets (2/3 grain) of emetine hydrochloride orally three times a day for 12 days. Total 24 grains in 12 days.

Particular care was taken to see that no tablet was cracked, the protective covering being important. Some tablets were passed in stools intact. No vomiting or toxic manifestations of emetine were encountered. All showed steady clinical improvement.

Nineteen adults and five children were re-checked 2-9 months after the treatment. Clinical cure was obtained in all. Parasitologically there was failure in one, E. histolytica persisted 7 months after receiving the drug.

P. V. GHARPURE.

PLEURITIC PAIN: USE OF INTRAVENOUS CALCIUM GLUCONATE IN ITS RELIEF. By I. L. Bennett W. Lathem. Am. J. Med. Sc. **215**: 431-433, 1948. Table 1, References 22.

The old belief is that pain in pleurisy is due to friction of two roughened surfaces. Clinical and experimental observations suggest a more complex mode of origin. The local analgesics like spraying the skin by ethyl chloride, intracutaneous, intrapleural infiltration of novocain, intercostal nerve block produces often prolonged and occasionally permanent relief of this pain while the local analgesics cannot act for more than a few hours. The authors suggest that the pain is due to spasm of intercostal muscles. These drugs abolish the spasm and relieve pain. Calcium gluconate is known to abolish muscle spasm. Authors tried 10% calcium gluconate 10-20 cc. intravenously in 25 cases of pneumonia and 5 cases of pulmonary infarction. There was relief in 27 cases of which 4 had permanent relief.

S. N. SHAH.

CENTRAL NERVOUS SYSTEM INVOLVEMENT DURING MUMPS. By J. W. Brown H. B. Kirkland, G. E. Hein, Am. J. Med. Sc. **215**: 434-441, 1948. Tables 2, Figs. 3, Refs. 30.

The involvement of central nervous system before, during or after an attack of mumps is well known. It may be due to virus of mumps or by activation of a neurotropic virus by the virus of mumps. The clinical signs are headache, nausea, vomiting, mental confusion, etc. To determine the manifest and non-manifest nervous system involvement the authors did regular lumbar punctures in 77 cases of mumps. 33.7% showed pleocytosis in C.S.F. while only 11.7% showed clinical signs of C.N.S. involvement. Among patients who had epididymo-orchitis 42% showed pleocytosis. Though most of the cases are benign, authors report one case who had severe C.N.S. involvement and had not completely recovered at the end of two and a half years.

S. N. SHAH.

SURGERY

OCCULT BONE METASTASES. Ralph Shackman AND C. V. Harrison: Brit. Jour. Surg. **35**: 385-389, 1948.

In a short paper the authors produce graphic evidence to demonstrate the little known fact that the marrow spaces of a bone may be invaded by grossly visible metastases without any radiographic evidence of alteration in architecture. By taking contact X-Ray pictures of vertebrae showing visible deposits they were able to show that in only 50% of the specimens so examined was any radiographic change noticed. The article is beautifully illustrated with coloured photographs of bony specimens and radiographs.

E. J. BORGES.

THE OCCURRENCE OF GASTRIC NEOPLASMS IN YOUTH. Block, Grief AND Pollard. Am. J. of Med. Sci. **215**: 398-404, April 1948.

The authors reviewed previous reports of gastric neoplasms in individuals below 30 years of age and state that the average figures range between 0.7% and 2.8% of all gastric cancers. At the University of Michigan Hospital this incidence in 1913 cases over a 20-year period has been 1.04%.

They stress the fact that all these cases had been diagnosed late because the possibility of a gastric neoplasm was not considered on account of the youth of the patient.

As no previous studies on the relative frequences of the various gastric lesions occurring in patients under 30 years of age have been published, the authors have undertaken the task and report their results.

During the 20 year period there were 73 cases of gastric lesions in patients under 30 years of age; of these 50 were benign ulcers, 20 were carcinomas, 2 were lymphoblastomas, and 1 was gastric lues. "This indicates that in this age group although gastric lesions are rare, when one does occur there is approximately a 30% chance that it is a carcinoma."

E. J. BORGES.

PATHOLOGY

THE PARATHYROID: A STUDY BASED, IN PART, ON SIXTY POST-MORTEM EXAMINATIONS WITH PRESENTATION OF A CASE OF HYPERFUNCTIONING ADENOMA. H. U. Stephenson & W. L. McNamara. Am. J. Med. Sc. 215: 381-397, 48. Figs. 17, Refs. 46.

The parathyroid glands were first described as a separate anatomical entity in 1880. They develop from pharyngeal pouches. In sixty post-mortem examinations performed by the author their position varied. Each gland weighed about 35mgm. It was very soft. It had a flimsy capsule, rich blood supply, and scanty nerve supply. The chief parenchyma cell is large polyhedral cell with acidophil cytoplasm and large round deep staining nucleus with abundant chromatin. When cytoplasm is replaced by vacuoles these cells are called water clear cells. These cells are arranged in anastomosing cords or large sheets. Occasionally they form acini containing colloid. Oxyphil cells are said to occur after puberty and increase with age.

Parathormone chiefly acts on calcium and phosphorus metabolism. Collip believes that it stimulates osteoclasts into hyperactivity. Albright believes that it lowers the renal threshold of phosporus. Serum phosphorus falls and calcium rises. There is unsaturation of blood of calcium phosphate leading to liberation of it from bone. This in turn is excreted. Serum alkaline phosphatase which is able to liberate inorganic phosphates from organic phosphate is derived from osteoblastic tissue and is a sign of bone disease and not hyperparathyroidism.

The diseases of parathyroids are (1) Idiopathic hypo- and hyperplasia. (2) Diseases like rickets and chronic nephritis which deplete blood calcium and produce secondary hyperplasia. Similarly, secondary hypoplasia may be due to injury or accidental removal of parathyroids. (3) Hyperfunctioning adenoma and hypofunction due to destruction of gland by secondary deposits.

Clinical manifestations of hyperparathyroidism are many and varied. Laboratory findings are increased calcium and phosphorus excretion and hypercalcaemia. Calcium deposit in the kidney parenchyma and pelvis may lead to renal impairment. X-ray examination shows osteoporosis and cyst formations.

The authors report in detail a case of hyperparathyroidism. The patient noted change in the shape of his chest and decrease in his height seven years ago. He was feeling weak and losing weight. Then he developed frequency and urgency of micturition for which his prostate was removed. Two years ago he had fracture of the neck of femur which was fixed with Smith-Peterson pin. This pin migrated into pelvis producing pain and diarrhoea alternating with constipation and at the time of admission a diagnosis of carcinoma of descending colon was entertained. There was fair degree of anaemia. Blood calcium was between 14-19 mgm. There was fair amount of renal impairment and blood N. P. N. varied from 50-200 mgm. X-ray showed osteoporosis and numerous cystic areas. E. C. G. showed atrioventricular block and myocardial damage.

He was operated and parathyroid adenoma was removed. He died on the 15th postoperative day. Necropsy revealed severe calcification of aorta, stone in gallbladder contracted kidney with numerous gritty areas, calcium deposits in alveolar septa of lungs. The parathyroid adenoma contained largely chief cells with islands of oxyphil cells.

THE LEUKOCYTOSIS OF DIABETIC ACIDOSIS. By J. L. Tullis. Am. J. Med. Sc. **215**: 424-426, 1948. Table 1, References 11.

Leukocytosis is common in diabetic coma and often independent of infection. A regular polymorphonuclear leukocytosis occurs proportional with induced extra cellular hypertonicity in animals. The author studied in seven cases of diabetic coma level of tonicity at the height of coma, and leukocyte counts at the height of coma, six hours later and after recovery. Absolute number of neutrophils was calculated from differential count and after correcting for haemoconcentration. In all the seven cases plasma was hypertonic and all had absolute polymorphonuclear leukocytosis. In six of them the molarity and leukocytosis were proportional. As the hypertonicity in animals was due to Na and Cl ions and in human beings due to hyperglycaemia it may be that hypertonicity is *per se* the cause of leukocytosis.

S. N. SHAH

VISCERAL LEISHMANIASIS COMPLICATED BY SEVERE ANAEMIA. Ralph F. Bowers & Thomas A. Haediake. Am. Jr. Trop. Med., Vol. 27, No. 6, Nov. 1947, pp. 699.

Four cases are reviewed. Fourth case is unusual. Anaemia usually not below 40% is visceral leishmaniasis. In the fourth case described here 102 blood transfusion each of 500 c.c. were required to save life in addition to adequate doses of pentavalent antimony, even then failed to maintain the haemoglobin level 20-40%.

Case :—A negro aged 23 years, had landed in North Africa on 1-1-43. Early in February 1944 illness began with fever and chills. R.B.C. 1.9 million, Hb. 50%, W.B.C. 1750, P. 32, E.S.R. 18. Quinine Penicillin, Sulphadiazine and transfusion were administered. Spleen three fingers. Splenic puncture on 144-44 L.D. bodies seen. Total proteins 7.8%, Alb. 3.1%, Glob. 4.7%, Formol-Gel+++. Antimony compounds—Neostibosan, anthiomaline, were used without effect. Spleen became larger and harder. Hb 6 grms. W.B.C. 1400. P 57%, sternal biopsy showed hyperplastic marrow and many inclusion bodies suggestive of L.D. bodies. Proteins 11.8 grms. Alb. 3.5, Blob 7.5, Platelets 200,000. Reticulocytes 7-10%. Icterus Index 12 units. Bilirubin 1.3 mgm.

He was transferred to another hospital and splenic puncture here revealed L.D. bodies. Next 16 months various treatments were given but blood count could only be maintained by repeated blood transfusions, total number of transfusions required being 85 each of 500 c.c.

W.B.C. now were 1000-4000 per c.mm. Spleen was below umbilicus.

On 11-12-45 splenectomy was done. Spleen weighed 3050 grms. Subsequently the blood changes were striking W.B.C. 22,900 per c.mm. R.B.C. 4,000,000 per c.mm. Hb 80%. In six weeks this was restored to normal. Spleen showed many areas of infarction. Histological examination revealed marked destruction of the splenic architecture diffuse proliferation of the reticular tissue and areas of fibrosis. Six hamsters were inoculated with the splenic pulp. All were positive for Leishmaniasis. At the end of the article there is a good bibliography which contains one reference.

P. V. GHARPURE

POST VACCINAL ENCEPHALITIS. G. Stuart, M.D. Bulletin of the World Health Organisation, Vol. I, No. 10, pp. 36-61, 1947-1948.

In this memorandum the papers that follow have been summarised.

Encephalitis of this nature could not be considered as resulting from the type of lymph used but from the previous introduction of the causal virus. There was no relation between occurrence of the complication and the time of the year when the vaccination was performed. Race and sex does not appear to influence onset. The complication however appears to occur more frequently in cold northern countries than in southern countries.

The first cases to be observed were by Heine (1860), and Jendrassik & Marie (1885), Conbay (1905). The subject drew the attention of workers with outbreaks in 1922 in England where 82 cases were recorded and in 1923-24 124 cases occurred in Netherlands. Sporadic cases were reported in Scandinavian countries.

The publication contains tables of incidence and case fatality.

Proportion of cases to total vaccination varies from 1: 3208 to 1: 27405. In England the incidence per year was as follows :—In 1922 11 cases; in 1923 51 cases. During period 1922-28 93 cases occurred of which 50% were fatal.

1927-28 65 cases with 32 deaths; 1933-34 4 cases; 1936-37 8 cases with 5 deaths; 1939 1 case; 1932-39 5 fatal cases.

Etiology :—(a) Due to activation of virus X which is present but dormant like herpes virus, and activated by vaccinia. (b) It is a part of vaccinia just as nephritis is to scarlet fever.

Prophylaxis :—No certain means.

(a) Performance of primary vaccination during the first two months of life. (b) Use of vaccine which is not too potent. (c) Vaccination at most by two scars. (d) Employment of subcutaneous and intracutaneous vaccination. (e) For older children and adults who have not been previously vaccinated a dose of vaccinal immune serum to be given at the same time of vaccination.

Treatment :—Use of whole blood or serum of a recently vaccinated person in a dosage sufficiently large and administered sufficiently early to provide the patient with effective amount of neutralising antibodies.

(b) Use of sodium pentothal 0.025 grms. with glucose administered intravenously

(c) Use of sulphapyridine, sulphathiozole or sulphadiazine with immune serum.

Condition often clears spontaneously.

P. V. GHARPURE.

PROTHROMBIN ACTIVITY OF "STORED HUMAN BLOOD." F. J. Schilling, A. D. Natale, L. A. Amill. Am. J. Med. Sciences, **215**: 415-418, 1948. Fig. 2, Ref. 19.

The authors have examined 50 stored human bloods every day for 21 days for prothrombin activity. They employed Link-Shapiro modification of Quicks method. This method is better as it measures prothrombin activity rather than prothrombin content. There was rise in prothrombin activity for the first four days. This may be due to disintegration of platelets. At the end of one week the activity was 84.8% twelve days 66.2%, and 21 days 47.7%. Though the amount of prothrombin in 500cc of blood is small, the whole blood transfusion within a week of storage may be useful in hypoprothrombinaemia of hepatacellular failure or decumarol toxicity.

S. N. SHAH.

PEDIATRICS

TOPICAL AND PARENTERAL PENICILLIN THERAPY IN RITTER'S DISEASE. Robert O. Warthen, and John C. Sherburme, J. Ped. 33: 717-74, 1948.

Four cases of Ritter's disease in white infants aged 9 days, 6 days, 6 days and 3 weeks are reported. Case 1 had a white cell count of 35,000 with 33 per cent eosinophiles and hæmolytic staphylococcus aureus was cultured from the skin lesions. Case 2 had 8,900 leucocytes with 7 per cent eosinophiles and the blood culture showed staphylococcus albus. All the four cases were treated with large doses of penicillin 30,000 to 50,000 units every three hours intramuscularly and liberal local applications of penicillin ointment every 6 hours. No clothes were put on the children and warmth was maintained by heat cradles. All the cases recovered. Penicillin was injected for as long as nine days and local application was used for 15 days. The authors recommend that this treatment should be continued for several days after complete recovery to avoid recurrence.

G. COELHO.

FAILURE OF GAMMA GLOBULIN TO PREVENT VARICELLA. Morris Schaeffar and John A. Toomey. J. Ped. 33: 749-752, 1948.

The authors compare the results in a series of children who were injected with 5 to 10 c. c. Gamma Globulin intramuscularly after being in contact with a case of chicken-pox with a control group who, though in contact, were not injected. Three series of trials were conducted and the gamma globulin injected 2 to 5 days after the primary case with the erupted lesion appeared. In their opinion gamma globulin is not an efficient prophylactic measure against varicella since it failed to prevent or modify the disease in two out of three controlled experiments.

G. COELHO.

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POSITIVE BACILLARY FINDINGS IN THE SKIN OF CONTACTS OF LEPROSY PATIENTS

N. Figueredo and S. D. Desai. *

INTRODUCTION.

Early in the course of work in the treatment and investigation of patients at the Clinic of the Acworth Leper Home, Bombay, the need for some system of follow-up of patients was acutely felt, as an appreciable number of patients ceased attending, and observation of the results of treatment, etc., was frequently interrupted.

It was practically impossible to carry out an examination of contacts of patients who attended the Clinic. Such examination could only be made on some of those who accompanied the patients on their first visit to the Clinic.

The system of Home Visits through Health Visitors, specially trained for the purpose late in 1942, was therefore introduced and has been described elsewhere[3].

The follow-up of patients through Health Visitors led not only to an extended knowledge of the disease in patients generally, but also brought accurate data on the examination of contacts within easy reach.

Thus, in addition to detection of early cases of leprosy from among the contacts as a routine a close study revealed positive bacillary findings repeatedly in 25 contacts, who surprisingly enough exhibited no signs of the disease.

The first of these was from among the few contacts examined before the system of Home Visits was introduced. This case was under observation for 7 years and was treated with Hydnocreol in 5 c.c. doses once a week for the first 2 years of this period. Positive bacillary findings, however, continued to be obtained throughout the succeeding 5 years.

The other 24 cases were discovered after a larger number of examinations of contacts was made possible through the efforts of the Health Visitors. 6 of these were treated with daily intravenous injections of glucose, 25 per cent. in doses of 25 c.c. for 3 to 4 months. At the end of this period all were negative for acid fast bacilli, but in 2 of them positive bacillary findings were again obtained after a negative period of 1 and 1½ year.

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* From Acworth Leper Home, Matunga, Bombay.

The remaining 18 positive contacts were not given any treatment, but were observed for periods varying from 1 week to 12 months.

A presentation of these 25 positive contacts and a discussion of the significance of the bacillary findings in them is the object of this paper.

EXAMINATION OF CONTACTS.

The Health Visitors endeavour to persuade as many contacts as possible to submit to expert clinical and bacteriological examination by the doctors at the Clinic. However, 50 per cent of the contacts are not in a position to do so, either on account of lack of time, or because of the inability to grasp the importance of such examination.

The following table gives the number of patients, their contacts and the results of investigation :—

TABLE I.

1.	Patients whose contacts were examined	217
2.	Number of contacts in the homes of patients in 1 above	1049
3.	(a) Number of contacts examined clinically and bacteriologically ..	573
	(b) Proportion of contacts examined (573 out of 1049)	54.62%
4.	(a) Number of contacts who showed clinical suspicion of leprosy ..	319
	(b) Proportion of contacts showing clinical suspicion of leprosy to total contacts examined (319 out of 573)	55.67%
5.	(a) Number of contacts from 4 (a) above who showed clinical and bacteriological evidence of leprosy	171
	(b) Proportion of contacts showing clinical and bacteriological evidence of leprosy in 5 (a) to total contacts examined in 4 (a) above (171 out of 319)	53.6%
6.	(a) Number of contacts from 3 (a) above who showed no clinical evidence of leprosy	254
	(b) Proportion of contacts who showed no clinical evidence of leprosy in 6 (a) above to total contacts examined in 3 (a) above (254 out of 573)	44.32%
7.	(a) Number of contacts from 6 (a) above who showed presence of leprosy bacilli in the skin (even though on careful examination no lesion of leprosy could be detected)	25
	(b) Proportion of contacts with positive bacillary findings in the skin to total contacts without any lesions from 6 (a) above (25 out of 254)	9.84%

It will be seen that 319 contacts with suspicious signs were examined clinically and bacteriologically at the Clinic, and 171 of them were found to be suffering from leprosy. 254 contacts did not exhibit any signs and symptoms, but in 25 of them acid-fast bacilli were detected in smears made from snips taken from the ear-lobe or the skin of the back or both. We find that the skin of the back in the middle line on either side of the spine gives positive results more frequently than any other site and is more convenient both to the patient and the doctor.

METHOD OF EXAMINATION.

The examination of contacts involves three main lines of investigation :—

(1) *Clinical*: Contacts are stripped and observed in bright sunlight. This is essential for detecting erythema, loss of hair, and when these are absent, slight variations in pigment and texture of the skin. Clinical tests for detecting sensory changes are carried out as follows :—(*a*) Tactile—a wisp of cotton is used to elicit tactile disturbance. (*b*) Thermal—two test tubes, one with tap water and the other with water heated to a temperature of 50° to 60° C. are employed to detect changes in thermal sensibility. (*c*) Pain—a pin is used for testing pain sense.

The 25 positive contacts examined did not show clinically, any macules, erythema, thickness or dryness of skin, loss of hair or sensory disturbances, nor did they complain of any symptoms referable to leprosy and they also did not present any signs of other skin diseases.

(2) *Bacteriological* :—The improved technique used and care exercised in the preparation and examination of smears and sections in recent years, has materially increased our knowledge of the disease.

Lowe[5], writing on Tuberculoid Leprosy, states, " when we first started a close study of these lesions, in very few of them could we find any acid-fast bacilli. Smears made by the ordinary 'slit' and 'clip' methods nearly always gave negative results. By examination of biopsy material we could find a few bacilli in perhaps 10 per cent. of cases examined. When, however, we began to examine lessons more carefully, searching for bacilli in not one, but if necessary in six or eight sections, the percentage of positive findings rose, and when as a result of careful study, we improved our staining methods, the percentage of cases in which we found bacilli rose to about sixty."

This observation is true not only of sections but also of the examination of smears from snips of skin lesions of neural cases. In the Acworth Leper Home, Bombay, the positive bacillary findings of 20 per cent. in neural cases rose to 43 per cent. when more careful examinations were made. It was found that at least half an hour was necessary for a thorough examination of a slide which showed 4 or 5 bacilli in 100 fields. The same care was exercised in the examination of contacts.

The procedure of making smears from snips of the skin and ear-lobe of contacts is as follows :—The skin and ear-lobe are washed with 5 per cent. carbolic lotion and later wiped with a swab of rectified spirit. Instruments—scalpels, forceps, etc.--are sterilised by boiling and later by passing them through the flame of a Bunsen burner for a few seconds. A small piece of skin, 2 to 3 m.m. deep, is taken and pressed on an unused, cleaned slide, and a smear is made. The scrapings from the cut surface of the skin are also added to the smear, which is fixed with heat taking care not to char it, and is stained as follows :—Carbol fuchsin is filtered on to the slide and allowed to remain for 20 minutes. The slide is then washed in running water and decolourised for a few seconds with a solution containing 5 parts of concentrated hydrochloric acid, 75 of rectified spirit and 20 of distilled water. The smear is then washed again with running water and counterstained with Loffler's Methylene Blue for one minute. Smears from nasal scrapings taken from the septum are also stained in a similar way.

In this manner smears from snips of the skin of the back and ear-lobe and nasal scrapings were taken and examined on 2 occasions in 5, on 3 occasions in 7, and 4 to 10 times in 13 of the 25 positive contacts during a period of from 1 week to 7 years.

(3) *Immunological* :—Cochrane[1] is of the opinion that a lepromin reaction (excluding the reaction produced by extraneous tissue material) can only be positive in the presence of a primary focus, and is therefore analogous to the Mantoux Test. His opinion is based on his observation, that a positive lepromin test in a monkey is not obtained without previously inoculating the animal with a nodule from a patient with leprosy.

In 9 of the 25 positive contacts the lepromin test was done, and all 9 gave positive results. Refined Lepromin of Dharmendra was used in order that any reaction produced by extraneous tissue material might be avoided. It may be pointed out that 7 of these positive reactors were contacts of lepromatous patients, 1 of a positive neural, and 1 of a negative neural case.

RESULTS OF EXAMINATION.

The results of careful examination of contacts (Table I) revealed that out of the 254 contacts, who exhibited no clinical signs and symptoms of leprosy, 25 showed evidence of acid-fast bacilli in the skin. Smears from snips taken from the skin of the back and ear-lobe, on from 2 to 10 occasions from each of these contacts, during a period of from 1 week to 7 years, showed 4 to 25 acid-fast bacilli in 100 microscopic fields in the skin of 5, and in both skin and ear-lobe of 20 of them. Smears from the nasal scrapings taken at the same time gave negative results in all of them.

The bacilli were : (1) acid-fast and alcohol-fast, (2) slightly curved rods with rounded ends, uniformly stained, or (3) slightly curved rods, thicker at the ends, not uniformly stained, giving a beaded or fragmented appearance, with pale staining connecting links.

Microphotographs, Figures 1 and 2, show the bacilli found in the skin of the back in 2 of the 25 positive contacts. (No. 12 and 19 of Table II).

In 4 of these positive contacts lesions developed later during the period of observation. These 4 cases are described below :—

(1) D. B., female, aged 30 years. Husband an Na_2s_2 case. (positive neural). No clinical lesion. Bacteriological examination made on 20-12-1939 gave positive results in the skin of the back and ear-lobe. This examination repeated on 9 occasions at intervals of 1 to 32 months gave positive results in the skin and ear-lobe on all occasions. 5 to 16 bacilli were detected in 100 microscopic fields. Nasal scrapings were negative throughout. 1½ year after the first examination, small hypopigmented macules began to appear on the neck and later on the legs. No sensory changes could be detected, but one of the lesions on the neck was positive for bacilli, the skin and ear-lobe also being positive at the same time.

(2) A. M., male, aged 19 years. Father an L_2N_3 case. No clinical lesion. Bacteriological examination made on 31-8-1946 gave positive results in the skin of the back. This examination repeated on 4 occasions, at intervals of 3 weeks to 4 months gave positive results in the skin on the first repetition, and in both skin and ear-lobe on the next 2 occasions. The last examination was negative. 5 to 8 bacilli were found in 100 microscopic fields. Nasal scrapings were negative throughout. 7 months after the contact was first examined, a hypopigmented raised circular macule, 1 inch in diameter, was observed on the right forearm. There was no sensory change at first, but after 3½ months, tactile and thermal sensory disturbances were demonstrable. Bacteriological examination of the lesion gave negative results, and the nose, the skin of the back, and ear-lobe were also negative for bacilli. Lepromin done 1½ months after the first examination gave a positive reaction.

(3) R. B., female, aged 40 years. Husband an Na_2s_2 case (positive neural). No clinical lesion. Bacteriological examination done on 20-3-1946 gave positive results in the skin. This examination repeated 5 times at intervals of 1 week to 4 months gave similar positive results on all occasions except the last. 4 to 8 acid-fast bacilli were found in 100 microscopic fields. The ear-lobe and nose were negative throughout. 5 small hypopigmented macules with disturbances of tactile and thermal sensations, were observed 12 months after the first examination on the lower extremities. Bacteriological examination of one of the lesions showed 6 acid-fast bacilli, but the skin of the back, the ear-lobe and nasal scrapings were negative. Lepromin done 7 months after the first examination gave a positive reaction.

(4) E. D., male, aged 50 years. Wife an L_2 case. No clinical lesion. Bacteriological examination done on 11-3-1946 gave positive results in the skin of the back and ear-lobe. This examination repeated on 5 occasions at intervals of 1 week to 3 months gave similar positive findings every time except the last. 5 to 11 acid-fast bacilli were found in 100 microscopic fields. Nasal scrapings were negative throughout. 8 months after the first examination 2 hypopigmented flat macules, each about 1 inch in diameter, were observed on the left arm and on the back. The tactile and thermal sensations were impaired. Bacteriological examination of the lesions gave negative results. Nasal scrapings, snips of the skin of the back and ear-lobe taken at the same time also showed no bacilli. Lepromin done 5½ months after the first examination gave a positive reaction.

A short description of the 25 positive contacts is given in Table II below :

TABLE II.

Contacts examined and found positive			Contact history		Bacteriological examination			Lepromin	Remarks.
Serial number	Register No. of Contact.	Sex and Age.	Contact with	Period of Contact	Number of occasions on which snips were taken and examined	Period of observation.	Results of examination of smears from snips		
1	699	Female, 30 years	Husband, Na_2S_2 (positive neural)	10 years	10 at intervals of 3, 4, 1, 3, 4, 26, 12, 1 and 32 months.	86 months	All positive in skin and earlobe. Bacilli 5 to 16 in 100 fields.	Not done	Treated with hydnocreol for 2 years. Developed small hypopigmented macules on neck and legs. No sensory changes in lesions which were positive for bacilli. Under observation.
2	3053	Male, 44 years	Brother: L_2	10 years	7 at intervals of 2, 2, 4, 2, 1 and 13 months.	23½ months	First 2 positive in skin and earlobe. Bacilli 4 to 14 in 100 fields. Subsequent 5 examinations negative.	Not done	Treated with glucose intravenously daily for 4 months. Not traceable after seven examinations.
3	3751	Male, 24 years	Sister: L_2 (neighbour L_2)	5 years	5 at intervals of 3, 3, 2 and 2 months.	10 months	First 2 positive in skin only. Bacilli 4 to 10 in 100 fields. Subsequent 3 examinations negative.	Not done	Treated with glucose intravenously daily for 4 months. Not traceable after 5 examinations.
4	3826	Male, 35 years	Mother: L_2	10 years	4 at intervals of 3, 9 and 5 months.	17 months	First positive in skin and earlobe. Bacilli 5 to 7 in 100 fields. Subsequent 3 examinations negative.	Not done	Treated with glucose intravenously daily for 3 months. Not traceable after 4 examinations.

TABLE II—(*Contd.*)

Contacts examined and found positive.			Contact history		Bacteriological examination			Lepromin	Remarks.
Serial number.	Register No. of Contact	Sex and Age.	Contact with	Period of Contact	Number of occasions on which snips were taken and examined	Period of observation	Results of examination of smears from snips		
5	3926	Male, 25 years	Brother : Na_2S_2 (positive neural)	5 years	5 at intervals of 3, 3, 7 and 3 months.	16 months	First positive in skin and earlobe. Bacilli 20 to 25 in 100 fields. Subsequent 3 examinations negative. Last examination positive in skin. Bacilli 10 in 100 fields.	Not done	Treated with glucose intravenously daily for 3 months. Not traceable after 5 examinations.
6	3953	Male, 25 years.	Father : Na_2S_2 (positive neural)	15 years	5 at intervals of 4, 4, 3 and 24 months	35 months	First positive in skin and earlobe. Bacilli 5 in 100 fields. Subsequent 4 examinations negative.	Not done	Treated with glucose intravenously daily for 4 months. Not traceable after 5 examinations.
7	4093	Male, 14 years	Brother : Na_2S_2 (positive neural)	3 years	5 at intervals of 3, 2, 8 and 6 months.	19 months	First positive in skin and earlobe. Bacilli 4 to 15 in 100 fields. Subsequent 3 examinations negative. Last examination postive in skin only. Bacilli 11 in 100 fields.	Not done	Treated with glucose intravenously daily for 3 months. Not traceable after 5 examinations.
8	4386	Male, 30 years.	Mother · L_2	5 years	3 at intervals of 2 months.	4 months	First 2 positive in the skin and earlobe, and the third in the skin only. Bacilli 5 to 20 in 100 fields.	Positive	Not traceable after 3 examinations.

TABLE II—(*Contd.*)

Contacts examined and found positive			Contact history		Bacteriological examination			Lepromin	Remarks.
Serial number.	Register No. of Contact.	Sex and Age	Contact with	Period of Contact	Number of occasions on which snips were taken and examined	Period of observation	Results of examination of smears from snips		
9	4775	Male, 42 years.	Brother : L_2	5 years	6 at intervals of 2, 2, 4, and 4 months.	12 months	All positive in the skin and ear-lobe. Bacilli 5 to 15 in 100 fields.	Positive	Not traceable after 6 examinations.
10	4876	Male, 27 years	Uncle : Na_2S_2 (positive neural)	1 year	3 at intervals of 2 and 1 weeks	3 weeks	All positive in the skin and earlobe. Bacilli 4 to 8 in 100 fields.	Not done	Not traceable after 3 examinations.
11	4877	Male, 35 years.	Brother : L_2	5 years	3 at intervals of 1 day and 4 months.	4 months	All positive in the skin only. Bacilli 5 to 7 in 100 fields.	Positive	Not traceable after 3 examinations.
12	4965	Male, 28 years	Wife : L2	3 years	5 at intervals of 3, 1, 4 and 13 months.	21 months	First 2 positive in the skin and ear-lobe. Next 3 in the skin only. Bacilli 8 to 10 in 100 fields.	Positive	Under observation.
13	4970	Female, 40 years	Husband: Na_2S_2 (positive neural)	10 years	6 at intervals of 1 week, 4, 3, 1 and 4 months.	12 months	5 positive in the skin only. Bacilli 4 to 8 in 100 fields. Last examination negative.	Positive	Developed 5 small hypopigmented macules with disturbances of tactile and thermal sensations. Lesion positive for bacilli.
14	4981	Male, 24 years.	Mother : L_2	5 years	3 at intervals of 2 months.	4 months	All positive in the skin and earlobe. Bcilli 5 to 10 in 100 fields.	Not done	Not traceable after 3 examinations.

TABLE II—(*Contd.*)

Contacts examined and found positive			Contact history		Bacteriological examination			Lepromin	Remarks.
Serial number.	Register No. of Contact.	Sex and Age	Contact with	Period of Contact	Number of occasions on which snips were taken and examined	Period of observation	Results of examination of smears from snips		
15	5062	Female, 13 years	Uncle : N_3 (positive neural)	10 years	3 at intervals of 1 and 7 months.	8 months	All positive in the skin and ear lobe Bacilli 5 to 11 in 100 fields.	Not done	Not traceable after 3 examinations.
16	5078	Male, 25 years.	Sister : Ns_2 (negative neural)	3 years	2 at an interval of 2 weeks.	2 weeks	Both positive in the skin and earlobe Bacilli 5 to 10 in. 100 fields.	Not done	Not traceable after 2 examinations.
17	5079	Male, 25 years.	Grand-mother : L_2 (Father : Nt2)	15 years	2 at an interval of 2 weeks.	2 weeks	Both positive in the skin and ear-lobe. Bacilli 4 to 6 in 100 fields.	Not done	Not traceable after 2 examinations.
18	5119	Male, 25 years.	Brother : N_3 (negative neural)	10 years	2 at an interval of 1 week.	1 week	Both positive in the skin only. Bacilli 4 to 6 in 100 fields.	Not done	Not traceable after 2 examinations
19	5201	Male, 27 years.	Sister : L_2	3 years	7 at intervals of 1, 1½, 3½, 2, 3 and 15 months	26 months	First 3 positive in the skin and ear-lobe ; next 4 positive in the skin only. Bacilli 4 to 17 in 100 fields.	Positive	Under observation.
20	5429	Male, 19 years	Father : L_2N_3	15 years	5 at intervals of 3 weeks, 3, 3 and 4 months	11 months	First 2 positive in the skin ; next 2 positive in the skin and earlobe. Bacilli 5 to 8 in 100 fields. Last examination negative.	Positive	Developed a hypopigmented raised macule on right fore-arm with impaired tactile and thermal sensations. Lesion negative for bacilli.

TABLE II—(*Contd.*)

Contacts examined and found positive			Contact history			Bacteriological examination		Lepromin	Remarks.
Serial number.	Register No. of Contact.	Sex and Age	Contact with	Period of Contact	Number of occasions on which snips were taken and examined	Period of observation	Results of examination of smears from snips		
21	5463	Male, 25 years	Brother : Na_2S_2 (positive neural)	5 years	2 at an interval of 4 months	4 months	Both positive in the skin and earlobe. Bacilli 4 to 5 in 100 fields.	Not done	Not traceable after 2 examinations.
22	5725	Male, 38 years	Uncle : NS_2 (negative neural)	3 years	3 at intervals of 1 and 5 weeks	6 weeks.	First positive in the skin and earlobe; second and third positive in the skin only. Bacilli 4 to 16 in 100 fields.	Positive	Under observation.
23	6544	Female, 45 years	Son : L_2	5 years	2 at an interval of 1 week	1 week	Both positive in the skin only. Bacilli 8 to 15 in 100 fields.	Not done	Not traceable after 2 examinations.
24	6580	Male, 16 years	Father : L_2 (Mother : Nt_2 Brother : Na_2t_2)	10 years	3 at intervals of 1 and 2 months	3 months	First and third positive in the skin only; second positive in the skin and earlobe. Bacilli 4 to 8 in 100 fields.	Not done	Not traceable after 3 examinations.
25	Obs/69	Male, 50 years	Wife : L_2	10 years	6 at intervals of 1 week, 1, 1, 3 and 3 months	8½ months	5 positive in the skin and earlobe. Bacilli 5 to 11 in 100 fields. Last examination negative.	Positive	Developed 2 small hypopigmented macules on left arm and back with impaired tactile and thermal sensations. Lesion negative for bacilli.

DISCUSSION

It might be opportune at this stage to discuss certain phases of leprosy which might be confused with the 25 contacts in whom the positive bacillary findings were made.

The "hazy" patches of Chiyuto and Rodrigues[1] and "juvenile leprosy" of Muir[6], termed "pre-lepromatous maculæ or incipient lesions of childhood" (and occasionally of adults) by Cochrane[1], and the earlier stages of diffuse lepromatous leprosy are the only stages that need be considered.

(*a*) In the pre-lepromatous or incipient lesions of childhood, the main characteristics as described by Cochrane are : small multiple, hypopigmented patches with the appearance and distribution of lepromatous rather than neural leprosy. That is, the lesions are slightly shiny indicating some erythema with the periphery fading imperceptibly into the surrounding normal skin. There is no nerve enlargement or anæsthesia of the extremities, and the lesions are negative to standard methods of examination. Lepromin is also negative.

(*b*) Diffuse lepromatous leprosy : These cases in the early stages are very difficult to detect because no actual lesions are demonstrable (Cochrane[1]). Cases with wide-spread infiltration have often escaped clinical detection even under expert examination, and yet bacteriological examination showed massive infection of the corium and even clumps of bacili in the superficial layers of the epithelium (Muir[6]). Constant features of this stage of leprosy are, the ease with which fairly large numbers of bacilli are found and the negative reaction to lepromin.

The above stages of the disease, and the positive contacts presented in this paper are tabulated below for comparison.

TABLE III

Type	Clinical findings	Bacteriological findings	Immunological findings.
Pre-lepromatous or incipient lesions of childhood.	Definite lesions, visible as hypopigmented areas with ill-defined margins.	Negative to acid-fast bacilli by standard methods of examination.	Negative to lepromin.
Early diffuse lepromatous leprosy.	No clinical lesions demonstrable.	Fairly large numbers of acid-fast bacilli.	Negative to lepromin.
Positive Contacts	No clinical lesions demonstrable.	Very small number of acid-fast bacilli.	Positive to lepromin. (9 out of 9)

It will be seen from the above table that the positive contacts differ from the two stages of the disease in two essentials: the number of bacilli, and the result of the lepromin test, and cannot therefore be classed as either of the two stages of leprosy mentioned.

What then is the significance of positive bacillary findings in individuals residing with leprosy patients? Are these persons in a very early stage of the disease? And if so, to what classification do they belong?

The acid-fast bacilli found, presented all the morphological and staining characteristics of M. Lepræ. Further, these individuals were all residing with leprosy cases. It may here be pointed out that of the 25 positive contacts 14 were in close association with lepromatous patients, 8 with neural cases in whom M. Lepræ could be demonstrated and 3 with neural cases in whom M. Lepræ were not detected. It is not suggested that the 3 negative neural cases were responsible for infecting their contacts. There was probably some lepromatous patient responsible for this damage both to the contacts and the neural cases—and some such source must be presumed to explain the causation of the disease in the neural cases—but we have not personally been able to trace such a source. Only those patients examined and seen residing with contacts have been mentioned.

The development of clinical lesions in 4 of the positive contacts is not without its significance. The lesions could have been caused only by the presence of M. Lepræ in the skin, and that the acid-fast bacilli found in the skin are the M. Lepræ concerned is therefore the logical conclusion.

Further, the lepromin (refined) gave positive reaction in 9 of the positive contacts, *i.e.* in all in whom it was done, and in the opinion of Cochrane "a lepromin reaction (excluding the reaction produced by extraneous tissue material) can only be positive in the presence of a primary focus, and is therefore analogous to the Mantoux Test".

Sorel[7] and Leboeuf[4] have found M. Lepræ in the lymph glands of apparently normal individuals living in close association with persons suffering from leprosy.

It is the hypothesis of Cochrane[1] that "when infection takes place one of three things may happen: (1) The person may never develop leprosy and thus no indication of a previous infection is available. (2) The person may develop leprosy which shows itself in clinical lesions which may remain stationary or disappear entirely either by themselves or as a result of the development of tissue immunity. (3) The lesions may progress and the person become an advanced case of leprosy."

The above is based on the theory that "the wandering cells of the body are probably able to deal by phagocytosis with considerable numbers of

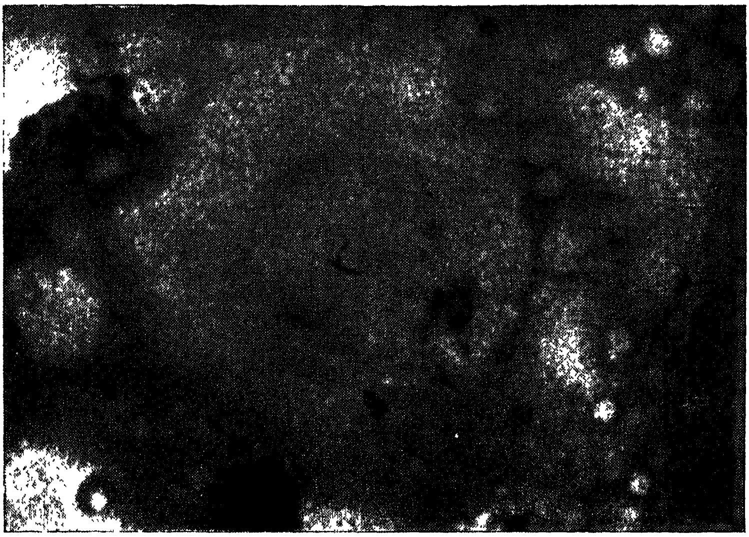

FIG. 1—Microphotograph of smear from skin of a positive contact showing 2 bacilli, one uniformly stained, the other fragmented in appearance.

FIG. 2—Microphotograph of smear from skin of a positive contact showing 2 uniformly stained bacilli.

bacilli, if introduced into the body; but if this is impossible because of the numbers of bacilli introduced by the original inoculation or inoculations or for some other as yet unknown reason, then the bacilli pass to the skin and clinical lesions make their appearance."

It is therefore not unlikely that bacilli exist in the skin for some time before clinical lesions develop, and hence the presence of M. Lepræ in the skin is not incompatible in the absence of clinical lesions. The 25 contacts described in this paper may therefore be classed as group (2) above with this difference that they have developed leprosy, which shows itself not in clinical lesions, but as a bacillary invasion of the skin, a stage earlier than any described so far.

The 229 contacts examined and found negative may be grouped under (1) above, for these persons must have received inoculation or inoculations of bacilli during their residence with the infecting patients, and yet "no indication of an infection is available."

There does not appear to be any informed opinion on the bacteriological examination of healthy looking contacts of leprosy cases, nor do we know whether such examinations are carried out as a routine procedure anywhere.

We believe that if a careful bacteriological examination of all contacts of leprosy patients in households is systematically carried out, many cases of the type described in this paper will be brought to light.

SUMMARY.

(1) A description is given of 25 contacts of leprosy cases presenting no clinical lesions of leprosy, but showing evidence of acid-fast bacilli in the skin. (2) The significance of the presence of acid-fast bacilli in the skin of the 25 contacts is discussed. (3) It is shown that these 25 contacts were not in any of the known stages of leprosy, but were probably in a phase of the disease earlier than any that has so far been described.

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RECTAL SWAB IN THE INVESTIGATION OF DIARRHOEAS IN CHILDREN

Eric Coelho *

In treating diarrhœas an accurate knowledge of their cause is very desirable. For this a history, carefully taken, a naked eye and microscopic examination of the stool are essential. In every case of diarrhoea the stools should be cultured, but the limitations of laboratory staff do not always permit this.

In investigating diarrhœas jn children, certain difficulties arise. One is in getting a fresh sample of the stool. This is particularly so with infants. The second is in obtaining samples of stools from the children attending the out-patient department, because they are children and because the parents are ignorant and illiterate. The samples brought are often dry or mixed with urine. In search of a procedure that would overcome these difficulties, the rectal swab was adopted. This gave a fresh sample when you wanted it, put no strain on unwilling parents to collect a stool, minimised the risk of interchanging the stools in the wards and above all took little time.

During World War II the rectal swab method of collecting fœcal material for examination was used very extensively to obtain material for cultures from the lower rectum. According to Manson-Bahr[4] the results were more satisfactory than those obtained by culturing freshly passed motions. Cruickshank and Swyer[2] used this method to collect material for the purposes of culture in cases of Sonne dysentery, and comparing it with samples from voided stools they reported that the rectal swab method gave a higher proportion of positive results. Hynes[3] studying the isolation of intestinal pathogens by selective media confirmed the findings of Cruickshank and Swyer and further found that the rectal swab was not inferior to fæces in obtaining cultures in cases of other intestinal infections. In the investigation reported in this paper there was no intention of culturing the fæces; the rectal swab was utilised only to collect the material for a routine microscopic examination.

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Apparatus required for collection of rectal swab are:—

(*a*) A proctoscope—It is very similar to the one used for adults, the difference being in the size of the bore, which is only $\frac{3}{8}$ of an inch in diameter;

(*b*) glass slides and cover slips.

(*c*) normal saline, iodine solution and soft paraffin;

(*d*) broom sticks to which cotton swabs are attached;

In the Byramjee Jeejeebhoy Hospital Laboratory we use a box with suitable compartments so that each of the above-mentioned articles can be kept in their proper places.

POSITION OF THE CHILD

Before describing the technique of taking the rectal swab, I would very much like to say a few words about the various positions the child may be held in, whilst introducing the proctoscope. As in adults, the left and right lateral positions can be used for children who are older and co-operative, but in infants it is rather difficult to hold them in these positions. Infants can be placed with their abdomen facing downwards on a table, with their mothers holding them in the lumbar region and across both the knees. This is quite a good position. Another position is to put the child on its back with mother holding the knees and flexing the thigh on the abdomen. It is a very convenient position for the mothers to hold the child, but at the same time it is also very convenient for the young child, who with the increase of abdominal pressure brought about by flexion of the thighs on abdomen and with the increase of rectal pressure by the introduction of the proctoscope, passes a stool with a force very similar to that of water coming out through a hose-pipe. The best position as far as an infant is concerned is the following: Let the mother sit on a chair, put the child face downwards on her lap; ask her to hold the child with one hand on the back and with the other across the knees.

TECHNIQUE OF RECTAL SWAB

On a clean slide place a drop each of normal saline and iodine solution at either end, by means of a pipette. Hold the proctoscope with the right hand, dip it in vaseline. Separate the buttocks with the left hand and introduce the proctoscope slowly with a steady pressure till it enters the rectum for about an inch or so. Then remove the obturator and stand at a respectable distance. Take the swab, introduce it inside the proctoscope; just give the swab a to and fro twist with the fingers. Pull out the swab and then withdraw the proctoscope. Rub the swab first on the saline and then on the iodine drop. Put the cover slips and see under the microscope. It is a very simple procedure occupying just a few seconds. Under the microscope the slide is first seen under the lower power, visualising the field in vertical directions, about 6 to 8 directions, and, later under the high power, the slide is seen diagonally in step form.

MATERIAL

A rectal swab was done on 440 patients of whom 310 came with a history of acute symptoms lasting not more than 15 days and 130 with symptoms of longer duration or with history of repeated attacks. Table 1 gives the results of the examinations.

TABLE 1—*Result of Examination of Rectal Swab.*

	Acute.	*Chronic.*
Pus cells	229	74
Macrophages	111	27
Giardiasis—vegetative	46	33
Giardiasis—cysts	6	13
Endamoeba Histolytica—vegetative	17	6
Endamoeba Histolytica—cysts.	5	7
Fat globules	58	20
Fatty acid crystals	38	10
RBCs	58	18
Ova—round worms	15	6
Ova—whip worm	5	3
Ova—hook worm	0	0
Nil	31	6
Charcot Leyden Crystals	2	3

In some patients in addition to the rectal swab fresh stools were examined. Table 2 gives the results of this investigation.

TABLE 2—*Comparison between Rectal Swab and Stool Examintion in Diarrhoeas (59 patients)*

	Rectal Swab.	*Stool*
Pus cells	48	27
Macrophages	18	16
Fat globules	11	19
Fatty acid crystals	7	7
Giardiasis—vegetative	6	7
Giardiasis—cysts	4	2
Endamoeba Histolytica—veg.	10	2
Endamoeba Histolytica—cysts	3	3
RBCs.	15	13
Nil	5	2
Ova—round worm	2	8
whip worm	0	3
hook worm	0	0
Charcot Leyden Crystals	1	1

Stools of every patient admitted to the Hospital are examined as a routine. In view of the findings mentioned above it was questioned whether a rectal swab would reveal more than a stool examination in patients without a history of diarrhoea, acute or chronic. Thirty patients were investigated in this way. Table 3 shows the results.

TABLE 3—*Comparison between Rectal Swab and Stool Examination in non-diarrhoea cases. Total number of patients 30.*

	Rectal Swab.	*Stool.*
Pus cells	2	1
Macrophages	1	0
Giardia	5	3
Endamoeba Histolytica—vegetative	0	0
Endamoeba Histolytica—cysts	3	1
Ova—round worm	4	7
hook worm	1	1
whip worm	2	1
Fat globules	7	9
Fatty acid crystals	2	4
Starch	2	7
Nil	15	8

DISCUSSION

Table 1 demonstrates that the rectal swab provides you with a sample of the rectal contents adequate to discover all the abnormal findings that one gets on examination of a stool.

Table 2 is more revealing. A good percentage of acute diarrhœas in children is due to a bacillary infection. Finding of macrophages and pus cells in the stools is strong evidence of this infection. The figures for macrophages are nearly equal while for pus cells the sample from the rectal swab is definitely better. The rectal swab gave a positive result for *Endamœba Histolytica* oftener than the stool, particularly for the active, vegetative forms. This will be quite in keeping with the accepted directive for stool examination in amœbiasis—a fresh stool kept warm; the rectum provides these facilities. Though the figures in Tables 2 and 3 are few, yet it is my impression after taking into consideration the previous experience of stool examination that examination of sample obtained by a rectal swab is better for the detection of giardia lamblia. On the contrary an examination of a voided stool is more profitable than the sample from a rectal swab when one is in search of round worm ova. While they were found in 15 stools they could be seen in only six rectal swabs. The ova stick to fœcal matter, and the paucity of this in the rectal swab may explain this disparity. The positive findings in the rectal swab were obtained when there was fœcal matter.

In the 'normal patients' the rectal swab detected more patients with giardia and cystic form of *Endamœba Histolytica* while the stools gave a higher positive figure for round worm ova. But while in 15 out of 30 patients the rectal swab failed to reveal anything, only 8 stools failed to do so.

The rectal swab has been of definite value in detecting infection with Endamoeba Histolytica.

These investigations also reveal—

1. The role of giardiasis in acute and chronic diarrhœas of children. Out of 310 acute diarrhœas 52 (16.4%) were due to this infection, and out of 130 chronic diarrhœas 46 (43%) were due to this. Giardiasis is an important cause of chronic and repeated diarrhœas. The youngest child in whom giardia were found was 14 days old.

2. The causes of acute diarrhoeas in the order of frequency are (a) infections, probably bacillary infections—pus cells in 229 out of 310 patients and macrophages in 111 out of them ; (b) fat indigestion, 58 patients with fat globules and 38 with fatty acid crystals ; (c) giardiasis—52 out of 310 patients (17%) ; (d) amoebiasis—22 out of 310 patients (7%).

The age group of the children suffering from these different causes is shown in Table 4. From that it will be seen that amoebiasis is an infection of older children. The youngest child in this series was 2 years old, though G. Coelho (personal communication) has found motile E. Histolytica in a child 15 days old. That the round worms may cause acute diarrhoea is well-known, but they do not get the first place. In this investigation only 15 out of 310 patients had round worm ova and of these some had other abnormal findings.

TABLE 4—*Age Groups.*

	up to 2y.	2y. to 4y.	4y. to 6y.	6y. to 8y.	8y. to 10y.	10y. to 12y.	above
Bacilliary ..	37	79	8	4	4	6	3
Giardiasis ..	25	32	17	8	12	4	..
Fat Globules..	43	15	..	..	..	..	..
Fatty acid Crystals ..	24	12	..	..	..	..	..
Amoebiasis ..	..	13	8	4	4	4	2

3. In the chronic diarrhœa signs of bacterial infection are still found in a good percentage. 74 out of 130 had pus cells and 27 out of 130 had macrophages. The giardia lamblia claim more victims (43%) and the percentage of amoebiasis rises (10%).

4. In 10% of patients a rectal swab may be negative. Hence a single examination is not sufficient.

This method of the rectal swab for obtaining a sample of the stool is without any danger, if a little gentleness and care is exercised. The youngest child in the investigation was 14 days old.

In my opinion this is an easy, quick and reliable method to obtain a sample of a stool in children and particularly in infants. The results of the examination of this sample are as satisfactory as a stool examination, and in some respects better. A "rectal swab" should form a routine procedure in a Children's Ward.

SUMMARY

The technique of the rectal swab in children is described.

This method has an advantage of ease, availability, and universal application, and gives a fresh sample.

The results of 440 rectal swabs in 310 patients of acute and 130 patients with chronic diarrhoeas are discussed. The samples were satisfactory and revealed sufficient information.

The results of the examination of rectal swabs are compared with those of the stools in the same patients. The rectal swab is better particularly for amoebiasis, giardiasis, macrophages but a stool examination was better for finding ova.

Whether rectal swab yields more information than a stool in normal cases was studied by an observation on such cases. There was nothing particularly in favour of the rectal swab.

The causes of acute and chronic diarrhoeas as disclosed by these examinations are infections, fat indigestion, giardiasis and amoebiasis. Giardiasis is an important cause in chronic diarrhoeas, fat indigestion in acute diarrhoeas.

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VITAMIN K *

PHYSIOLOGICAL STUDIES

D. V. S. Reddy †

NOMENCLATURE

Unlike the names of the other vitamins, usually indicated by the letters of the Anglo-Saxon Alphabet, A,B,C,D, with subnumerals where necessary, like B_1, B_2, B_6, etc., the name of Vitamin K is an abbreviation of the very expressive and descriptive term "Koagulations Vitamin" in the German and Scandinavian languages, in which the word coagulation is spelt with a K. Henrich Dam, the discoverer of the Vitamin, working in Copenhagen, naturally proposed that the newly-discovered accessory food factor (deficient dietary factor of chicks) be named Vitamin K. (Koagulations Vitamin). Rosenberg (1942)[32] gives a list of other names, commonly used for denoting this Vitamin.

Vitamins K.
Phylloquinones.
Coagulation Vitamin.
Prothrombin factor.
Antihæmorrhagic Vitamin.

Though it was originally considered as one substance, recent investigations have established that there are not only 2 or more natural compounds but also an increasing number of synthetic analogues. Hence, the new and more expressive term, "Group of Vitamins K" recommended by Rosenberg. On the other hand, it is unscientific to call the Vitamin antihæmorrhagic vitamin, as it cannot stop hæmorrhages, except in hypoprothrombinemia and even then, only when the liver is healthy.

DISCOVERY OF VITAMIN K

The story of the discovery of the vitamin K is itself very interesting, one investigation leading to new and unexpected clues and surprising results of far-reaching significance, as the following brief summary reveals. (Butt and Snell, 1941)[11].

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* Part of the Thesis submitted to the University of Madras for the degree of M. Sc., (Medical Faculty).

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> "Between 1929 and 1934, Dam and Schonheyder published several papers dealing with a deficiency disease of chicks, a disease which resembled scurvy and which could not be prevented by the administration of ascorbic acid. They ascribed this disease to lack of particular antihæmorrhagic factor (or factors) in the diet. Dam first observed a marked tendency of these fowls to bleed and suggested that since a diet containing certain common foodstuffs did not produce this disease, a new dietary factor must be involved. A syndrome consisting of bleeding from the base of pin feathers and of hæmorrhages in muscles, under the skin and in the abdomen was also reported independently by other workers. These later investigators suggested that this scurvy-like disease might be caused by an absence of Vitamin C. in the diet, since it could be cured by feeding the fowls fresh cabbage but Dam and Schonheyder found that Vitamin C. administered orally, did not affect the disease. Schonheyder, in 1935, reported that clotting of blood of chicks suffering from this type of hæmorrhagic diathesis was enormously retarded. Additional investigation by Dam led to the discovery that the deficient dietary factor was a fat soluble Vitamin, occurring in hog liver, hemp seed, certain cereals and vegetables . . . Dam also found that this Vitamin was not identical with either Vitamin A or B and that though it resembled Vitamin E., with respect of solubility and resistance to heating in air, it was different in that large quantities of Vitamin E did not afford protection against the hæmorrhagic disease of chicks."

Therefore, the necessity for a new accessory food factor was demonstrated. The new Vitamin was called Vitamin K (Koagulations Vitamin) as it had very prompt and perceptible influence on the coagulation of blood.

DISTRIBUTION IN NATURE

The pioneer experiments established that Vitamin K occurs in plant and animal tissue. Later investigations have shown that it is widely distributed in nature, and is found not only in green leaves but also in bacteria (B. *subtilis*, B. *coli*), not only in animal tissues but also in feces of man (probably due to bacterial content) and excreta of animals, like rat and of birds, like chicks.

One of the earliest and complete reviews of the occurrence of the Vitamin in Nature is given by Brinkhous (1940).[10] Writing on plants tested for the vitamin, he says:

> "Alfalfa and Spinach are very rich in Vitamin. Other plants having a high natural content are cabbage, cauliflower, kale, carrot tops, soya bean oil, nettle, chestnut leaves, pine needles, and seaweed. Less potent are tomatoes, hemp seed, and orange peel. Green leaves tend to be specially rich in the Vitamin while leaves which grow in the dark contain much less vitamin K. Also, fruits, seeds and roots, contain considerably less vitamin K than do green leaves."

SOURCES AND DISTRIBUTION OF VITAMIN K.

(From "Vitamin K." by Butt and Snell-1941).

Plants	*Activity.* (scale of four).
Chestnut leaves	4
Spinach	4
Cauliflower	3
Cabbage	3
Alfalfa	2
Tomato	1
Soya bean	1
Hemp seed	1
Cereals (wheat, oats, corn)	1
Animal Tissues	
Tissues dried: Hog, dog, chicken, man	1
Feces, Human or Chick	2
Urine of humans	nil
Bacteria.	
Escheria Coli	2
B. Subtilis	2
Staphylococcus aureus	2

VITAMIN K. CONTENT OF SOME FOOD MATERIALS.

(From Bicknell and Prescott's Monograph on Vitamins in Medicine, Second Edition, 1946/8.

	Dam Units per 100 *grams.*
Putrified fish meal	90000
Chestnut leaves	80000
Cabbage leaves	40000
Spinach leaves	55000
Cauliflower	40000
Feces	30000
Alfalfa	20000 to 40000
Different kinds of alga	13000 to 17000
Tomato Green	10000
„ Ripe	5000
Liver (Pork)	5000 to 10000
Liver (Poultry)	300
Peas, fresh	3500
Fish meal	less than 500
Cereals	500 to 4000
Human Milk	0 to 200
Cow's Milk	very little
Egg Yolk	very little

The best animal sources of the Vitamin never contain more than 10% of that present in alfalfa. Liver and lungs have less. Human urine contains no Vitamin K even after consumption of diets rich in Vitamin K.

Bacteria can synthesize Vitamin K; 0.6 to 2 grams of bacteria per kilo of basal diet will protect chicks against Vitamin K deficiency. Some bacteria are as potent as alfalfa. Moulds, yeast and fungi contain no Vitamin K. Most putrified animal and plant material contain high amounts due to bacterial growth.

Two special facts deserve to be mentioned, if not emphasized. One relates to the vegetable source and the other to animal source. Although green leaves are specially rich in vitamins, leaves which grow in the dark contain much less Vitamin K. The chlorophyl containing parts of the plant usually have the largest amount of Vitamin K.

In the animal body, small amounts may perhaps occur in all parts. In chicks maintained on normal diet, all the organs tested were found to contain the vitamin, in appreciable amounts. Hog's Liver contained a fair amount of this vitamin and is said to be the richest animal source. The relatively low concentration of Vitamin K in livers of different animals has been noted. Bile also does not have any vitamin activity.

EARLY METHODS OF PREPARATION OF NATURAL VITAMIN CONCENTRATES

Concentrates were first made by the extraction of dried alfalfa with hexane (Almquist and Stokstad, 1936)[3] and with acetone (Dam and Schonheyder, 1936)[16]. Later, it was made from either extracted fish meal or rice bran which was subsequently moistened and allowed to putrify slowly (Almquist and Stokstad, 1937)[4].

The later developments and chemical processes concerned with purification, isolation and study of structure by degradation experiments are too complicated and lengthy to be described here, in a paper dealing with the physiological aspects of the Vitamin.

CHEMISTRY OF VITAMIN K. COMPOUNDS

The discovery by Almquist and Stokstad[3] that alfalfa meal is a potent source of Vitamin K led to numerous attempts to isolate the substance by taking advantage of certain chemical properties of the vitamin such as differential solubility, adsorption, elution and molecular distillation. Karrer and associates[26] were the first to achieve the isolation of Vitamin K in pure or almost pure form in 1939 obtaining it as yellow oil. But, very soon it was apparent that more than one compound possessed Vitamin K activity. It was conjectured that there may exist a number of analogues, closely resembling the Vitamin K isolated from alfalfa. MacCorquodale, McKee and co-workers[29] isolated in 1939 two distinctly different compounds from alfalfa meal and putrified fish meal respectively. The Vitamin obtained from alfalfa was called Vitamin K_1 and that from fish meal Vitamin K_2. This nomenclature has been widely adopted and even extended.

The isolation of Vitamin K_1, in its turn, stimulated work on its structure. As a result of the work of Doisy (1939)[19] Almquist and Klose (1939)[2] Fieser and his collaborators (1939)[22] the structure of Vitamin K_1 was established. It is 2-methyl-3-phytyl-1: 4-naphthoquinone.

Soon after Vitamin K_2 was isolated from putrified fish meal as a light yellow crystalline solid with a biological potency of about 2/3rds that of Vitamin K_1 Binkley and co-workers (1940)[9] identified its structure. It is a 2-methyl-3-difarnesyl-1-:4-naphthoquinone.

SYNTHETIC ANALOGUES OF VITAMIN K.

Many compounds chemically related to Vitamin K_1 were reported to show anti-hæmmorrhagic action. The first Vitamin K analogue, with anti-hæmmorrhagic potency, was discovered by Almquist and Klose (1939)[2] who found that phthiocol, a compound originally isolated from tubercle bacillus had a slight Vitamin K action. Its structure is 2-methyl-3-hydroxy-1:4-naphthoquinone.

Most of the analogues are derivatives of 1:4 napthoquinone or of 1:4 naphthohydroquinone. One of the most exhaustively studied compounds is official in the British Pharmacopœia as menaphthone and in United States of America as Menadione. It is said to have a high anti-hæmmorrhagic potency. It is destroyed by exposure to light. As it is only slightly soluble in water, it is not suitable for intravenous use. But it has been applied cutaneously in fatty base and is said to have been absorbed (De Beer *et al.* 1941)[18]. It is 2-methyl-1: 4-naphthoquinone. A number of derivatives have been prepared from Menadione. One of them is 2-methyl-1:4-naphthohydroquinone diacetate- (Acetomenaphthone B. P. C.). It is more stable than menaphthone but has the disadvantage of not being water-soluble.

NATURALLY OCCURRING COMPOUNDS OF VITAMIN K.

Rosenberg's authoritative statement on this subject may be quoted here :

> "The existence of only 2 naturally occurring Vitamin K of high activity, namely, Vitamins K_1 and K_2, has been proved with certainty. Phthiocol, a naturally occurring compound is also somewhat active but in considerably higher amounts. The inclusion of this compound in the class of naturally occurring Vitamins K depends upon the proof that this compound is not an artefact from the alkaline hydrolysis procedure used for its isolation. It is, however, conceivable that besides Vitamins K_1

and K_2 other members of similar structure occur naturally, especially of the type with β-unsaturated isoprenoid side chains in the 3-position of 2-methyl-1, 4-naphthoquinone, such as 3-farnesyl-or 3-geranyl-derivatives.

Indication of the occurrence of at least one other factor has been obtained through the isolation of colourless fractions. This factor is highly active and resembles in its behaviour the oxides of Vitamin K. It is, therefore, possible that this compound or compounds are oxides obtained during the procedure of isolation."

WATER-SOLUBLE COMPOUNDS

Water-soluble and even stable compounds of Vitamin K have been prepared with varying combinations. Amongst these, the following have been used clinically (Bicknell and Prescott, 1946)[8].

Sodium Salt of 2-methyl-1; 4-naphthoquinone-3-sulphonic acid
Sodium 2-methyl-1: 4-naphthohydroquinone diphosphoric acid ester,
4-amino-2-methyl-1-naphthol (Vitamin K_5)
4-amino-2-methyl-1-naphthol and 1-amino-2-methyl naphthol hydrochloride
1:4 dehydroxy-2-methyl-3-naphthaldehyde
2-methyl-1, 4-naphthohydroquinone bisulphite
2-methyl-1: 4-naphthohydroquinone dibutyrate.

BIOGENESIS.

Rosenberg gives a brief account of biogenesis of Vitamin K.:—

"The Vitamins K are synthesized by plants and by certain microorganisms. In plants, the site of synthesis is in the green leaves. Thus the tops of carrots contain a considerable amount of Vitamin K while the roots contain practically none. The synthesis is greatly influenced by sunlight. Peas grown in the dark contain only small amounts, while control plants raised in light contain considerably more. The outer leaves of cabbage contain about four times more vitamin K than the inner leaves.

"The synthesis of Vitamin K_1 is presumably accomplished by methods similar to those used in the laboratory, that is, using phytol and methyl-naphthoquinone as building units. Vitamin K_2 is synthesized in certain microorganisms which live on Vitamin K-free diets. Colibacteria synthesize Vitamin K on a synthetic medium which contains as organic constituents only glucose, citrate and asparagin."

SPECIFICITY.

A vast amount of work was done to elucidate the specificity of the Vitamin K action. Rosenberg states that the following conclusions can be drawn.

"The quinones may be converted into the corresponding hydroquinones, their esters and ethers, without essential loss of efficacy as long as the derivatives can be reconverted into the quinones under more or less simple conditions which also may occur in the organism. The unsubstituted benzene ring of the vitamin molecule cannot be substituted without loss of activity. The 2-methyl group cannot be replaced by hydrogen or higher alkyl groups without considerable decrease in activity. The substituents on the 3-position, however, can vary considerably and the change in efficacy is only slight. The most remarkable fact is that when the substituent in 3-position is hydrogen, that is, when 2-methyl-1, 4-naphthoquinone is tested, an activity of from two to four times that of Vitamin K_1 per weight unit is observed. This unique activity of 2-methyl-naphthoquinone has caused widespread interest which led to the introduction of this compound into clinical therapy. Its unusual efficacy has been explained by the hypothesis that this compound itself does not act as a Vitamin in the organism but that it is converted in the organism into a quinone of the true Vitamin K. type. On the other hand, it has been postulated that the Vitamins K_1 and K_2 owe their activity to their degradation in the organism to 2-methyl-1, 4-naphthoquinone (Almquist 1941)[1]. While the later hypothesis appears less attractive no experimental proof for the validity of the former can be offered other than the fact that such a synthesis is easily accomplished in the laboratory and that the building units for a side chain of the Vitamin K_1 or K_2 type are readily available.

The effect of variations of the side chain in 3-position are noteworthy. A double bond in the by-position contributes to the potency while unsaturation at points more remote from the quinoid nucleus is without influence. A branched side chain, built from isoprene units is more active than a strictly straight chain, and maximum activity is reached when some 20 or 30 carbon atoms are present."

Fieser and Co-workers (1939)[22] put forward the view that the anti-haemorrhagic activity of Vitamin K and its analogues is related to the quinone structure. On the other hand, Shemiakin *et al.* (1943)[36] question the above opinion and advance the suggestion that the activity is the result of the oxidative bio-decomposition to phthalic acid within the body. This view is supported by the observation that they are readily transformed into phthalic acid on heating with water. The latest position with regard to our knowledge on this aspect has been summarised by Bicknell and Prescott (1946) in the following paragraph :—

"An intact benzene ring in the Vitamin K. molecule is essential for activity; if it is substituted activity is lost. The 2-methyl group is also essential and cannot be replaced by hydrogen or by other groups without serious loss of activity. The quinone structure is not essential *i.e.* the hydroquinones are almost as active, and the quinone oxygen can be replaced by other groups such as amino and aldehyde. The side chain in the 3-position can be eliminated without loss of activity. In fact the most active compounds are derivatives of 2-methyl-1: 4-naphthoquinone, in which the side chain is entirely replaced by hydrogen. It has been suggested that vitamins K_1 and K_2 owe their activity to their degradation to 2-methyl-1: 4-naphthoquinone within the body."

RELATIONSHIP BETWEEN THE NEW VITAMIN AND THE CLOTTING OF BLOOD

Schonheyder (1935)[34] was the first to observe, after the discovery of Dam, that the blood of chicks suffering from the nutritional haemorrhagic syndrome had a prolonged clotting time.

It was also Schonheyder (1936)[35] who suggested first that the prolonged clotting time resulted from hypoprothrombinemia.

Dam, Schonheyder and Tage-Hansen (1936)[17] confirmed these findings. They were unable to isolate prothrombin from the blood of vitamin K-deficient chicks, though it was found to be presnt in the blood of normal chicks. Prolonged clotting time was due to low plasma prothrombin. They also noted that an aqueous emulsion of vitamin K. failed to restore clotting time to normal, when added to blood plasma-thromboplastin mixture. Vitamin K had no thrombin-like activity.

Quick (1937)[31] observed a progressive fall in prothrombin in the blood of chicks on a vitamin K deficient diet. A distinct haemorrhagic tendency developed when low prothrombin levels were reached. Both low prothrombin and haemorrhagic tendency were cured by administration of foodstuffs rich in Vitamin K.

Finally in 1937 it was shown that mammals and man may develop Vitamin K deficiency with its associated hypoprothrombinaemia and haemorrhagic tendency, not only due to a diet deficient in the vitamin but also in conditions associated with absence of bile in the intestine. In the dog and rat this was achieved by an experimental biliary fistula. In experimental animals, the necessity for bile has been demonstrated in the rat and dog. (Greaves and Schmidt, 1937)[24]; (Smith et al, 1938)[38]. In man, such deficiency was observed in the cases of jaundice and biliary fistula. (Warner *et al.*, 1938)[41].

PHYSIOLOGY OF VITAMIN K.

Vitamin K is usually present in varying amounts in food ingested. Apart from this, there is always certain amount of Vitamin K synthesized by the micro-organisms in the bowels of animals and men, living on ordinary and adequate foodstuffs. Since the natural vitamins are fat-soluble compounds, they are absorbed only in the presence of bile salts (Greaves and Schmidt, 1937)[24]; (Butt, Snell and Osterberg, 1938)[12]. The special role of desoxy-cholic acid is stressed by Schmidt (1938)[33]. In addition to adequate amount of bile, the normal digestion of fat is also necessary for Vitamin K absorption. Intestinal lesions also interfere with vitamin K absorption. Elliot and Isaccs (1940)[21] have noted that mineral oil administered along with vitamin K interferes with normal absorption from the intestinal tract.

The fact that certain water-soluble compounds possess Vitamin K activity has raised the question as to whether or not these substances are absorbed from the intestinal tract in the absence of bile. Smith and Owen (1940)[37] have shown that oral administration of 4-amino-2-methyl-1-naphthol to patients suffering from chronic obstructive jaundice led to an increase in the level of prothrombin. Similar results were reported by Warner and Flynn (1940)[42] on administration of the potassium salt of the disulfuric acid ester of 2-methyl-1, 4-naphtho-hydroquinone to Vitamin

K-depleted bile-obstructed rats. Morse and Schmidt (1941)[30] pointed out that both phthiocal (2-methyl-2-hydroxy-1-, 4-naphthoquinone) and menadione are absorbed from the intestinal tracts of rats with bile fistulas and that desoxycholic acid is not necessary to insure the absorption of these compounds. But it was observed that the effectiveness of menadione taken by mouth is increased by the taking of desoxycholic acid or bile salts even in the absence of jaundice.

Rosenberg makes the statement that Vitamin K is to be found only in very small amounts—apparently only during times of transport—in blood but in some larger amounts in livers. The amimal organism, he says, had apparently no storage organs for this vitamin. "The body appears to metabolize the compound fairly rapidly." The mechanism of the metabolism is not known. The vitamin is not excreted through the kidney even if large doses are given. Considerable amounts of vitamin are found in the feces and this is believed to be due to bacterial synthesis in the intestinal tract.

Vitamin is secreted in minute amounts in milk and stored in eggs. There is apparently, as Rosenberg suggests, a special mechanism which regulates the passage of vitamin through the placenta. He also adds that it has been generally observed that a pregnant women just prior to parturition have increased need for vitamin K. The hypovitaminosis developing in new-born infant is considered physiological. Severe degrees of hypoprothrombinemia, leading to fatal hemorrhages may be prevented by feeding vitamin K to the infant immediately after birth or better still by giving Vitamin K. to the mother in advance.

PHYSIOLOGICAL ACTION OF VITAMIN K

The physiological action of Vitamin K is stated briefly in one sentence. It is necessary for the maintenance of normal blood coagulation. Though a few reports have appeared indicating its role in growth of laboratory animals (rats, etc.) and in the adjustment to temperature control, etc., these require further confirmation.

According to the classical theory of Morawitz two different phases are involved in the process. The first phase is the conversion of prothrombin present in the plasma into thrombin in the presence of calcium ions, through the action of another enzyme, thromboplastin which is a normal constituent of cells but not of blood.

The only effect of Vitamin K deficiency is a lowering of the prothrombin concentration in blood. (Dam, 1935;[13c] Schonheyder, 1935 and 1936[34], [35]). But Vitamin K is not identical with prothrombin. Vitamin K added to blood does not alter the blood coagulation time *in vitro* experiments. (Dam *et al.*, 1938)[15]. Vitamin K is also not a constituent of prothrombin as it has been proved that fractions of prothrombin do not have vitamin K effect. (Schmidt, 1938)[33]. The only physiological evidence is that Vitamin K influences the level of prothrombin. It is, therefore, assumed that vitamin K is involved in the prothrombin formation. The formation of prothrombin is accomplished in the liver (Schmidt, 1938;[33] Snell, 1939[39]). Partial extirpation of the liver markedly reduces prothrombin level in blood (Andrus, 1939;[5] Warner, 1938[40]). Clinically, Vitamin K deficiency has been observed even when the diets were adequate in vitamin K content, in cases of liver damage such as cirrhosis, hepatitis, atrophy and carcinoma. And it has been further observed that in all these cases of liver damage the prothrombin concentration could not be influenced by the administration of vitamin K given orally, or injected intravenously.

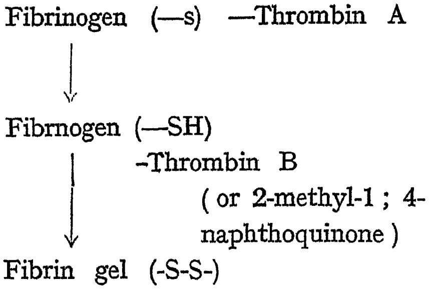
Vitamins K are required by all animals experimentally investigated: chick, duck, goose, canary, pigeon, turkey, rat, rabbit, mouse, dog and man. But the actual amount of this vitamin required by different species is unknown. Amounts varying from 1 mg. to 10 mg. have been recommended in human therapy. Increased amounts are also needed by pregnant and lactating women.

The mechanism of the Vitamin K action is still a mystery. One suggestion made is that the quinone structure of the Vitamin takes part in an oxidation reduction system involving the oxidation of SH groups to-S-S linkages (Bernheim, 1940)[7]. Baumberger (1941)[6] has advanced the hypothesis that the formation of blood clot also involves an oxidation of SH groups of fibrinogen to-S-S groups in fibrin.

MECHANISM OF VITAMIN K. ACTION

Lyons (1945)[27] has recently advanced a new theory, based on polarographic and chemical analysis of thrombin and fibrinogen, to account for the action of Vitamin K in the clotting mechanism. Thrombin can be divided into two active components, A and B, neither of which alone will cause fibrinogen to clot, although a mixture of the two will do so. Thrombin A reacts with fibrinogen liberating thiol groups (SH) to form an intermediate, fibrinogen B, between fibrinogen and fibrin. This has been isolated and can be clotted by thrombin B to form a fibrin gel, or by minute amounts, 1 microgram of 2-methyl-1; 4-naphthoquinone in 50 per cent. alcohol. In the clotting process it is considered that the thiol groups unite to form disulphide linkages-(-S-S). Microscopical examination of the gels produced by either method reveals no difference between the two. Lyons states that vitamin K is either a prosthetic part of thrombin B, or that it converts a protein fraction into an oxidation-reduction system with a potential in the neighbourhood of that of Vitamin K. When digested with trypsin thrombin gives a colour reaction characteristic of naphthoquinone, so that the former suggestion is quite likely.

The reactions postulated by Lyons are illustrated by the following scheme:—


Fibrinogen (—s) —Thrombin A
Fibrinogen (—SH)
-Thrombin B
(or 2-methyl-1 ; 4-naphthoquinone)
Fibrin gel (-S-S-)

NEED FOR PHYSIOLOGICAL STUDIES ON VITAMIN K

The discovery of Vitamin K. stimulated many scientific workers in Europe and America to undertake pioneer investigations in numerous directions. The chemists and bio-chemical laboratories and experimental biologists very soon established the essential basic facts, *viz.*, that it is a fat-soluble vitamin, that lack of this vitamin produces defective coagulation due to lowering of the prothrombin level in circulating blood and that the deficiency can be quickly corrected by the administration of natural substances like alfalfa or concentrates from certain vegetable and animal sources. The chemists persevered in their study of the chemical nature of the new vitamin, isolated and identified two substances, which had similar physiological effect but differed slightly in their chemical structure. Further work led to the interesting discovery that there were many synthetic compounds which were analogues of vitamin K. But there was still one defect, *viz.*, that these compounds were mostly insoluble in water, not absorbed by the alimentary tract without the presence of the bile and could not be adminstered intravenously. Intense team-work in different laboratories proved fruitful and water-soluble vitamin compounds were soon synthesized. The study of these new water-soluble compounds was conducted mainly along pharmacological and toxicological lines or in the prevention and cure of coagulation defects.

A large number of investigations have been conducted on the methods of producing vitamin K deficiency either by giving special diets or interfering with the absorption from the alimentary tract by ligaturing the bile duct or establishing a bile fistulæ, internal and external or by giving liquid paraffin daily or the inclusion of 1% to 2% of sulpha drugs in the experimental diet or by cecectomy.

Some amount of work has been done to establish the role of liver in the metabolism and utilization of Vitamin K in the formation and maintenance of the normal level of prothrombin in the animal organism. Animal experiments in which the liver was damaged by various drugs as well as numerous clinical conditions of the liver have been carefully studied, to prove that there is a definite lowering of prothrombin in spite of the supplies of Vitamin K. A few investigations were done to remove portions of the liver in animals and demonstrate the resulting fall of prothrombin in blood. A few histopathological studies have also been reported.

But the physiology of Vitamin K is still a mystery. Physiological studies of Vitamin K could not be but limited in number and scope, as long as the product was a fat-soluble one, which could not be administered intravenously or used for studying the physiological responses of various systems or organs in the intact animals or for testing the reaction of the isolated organs and segments, under different experimental conditions. Discovery of the water-soluble synthetic compounds with vitamin K activity has rendered possible a new line of research which has been till now neglected. Though Vitamin K was discovered in connection with coagulation defects, though its essential role is in the production and maintenance of normal level of prothrombin, very little is known of its physiological effects on other important systems of the body. It may be recalled that whenever a new vitamin was discovered, attention was focussed mainly on the original observation, till accidental discoveries by workers in entirely different fields gave new and unexpected clues compelling the revision of the earlier views, and starting fresh investigations. Vitamin A and its role in vision, Vitamin B complex and its role in gastro-intestinal tract, Vitamin C and its role in the erythropoiesis, Vitamin E and its effects in muscular dystrophy are all later advances, unconnected with the facts established in the early stages.

A powerful compound which can, in such minute traces, stimulate the liver to produce prothrombin cannot be expected to be absolutely without any effect on any other system or organ, in the animal organism.

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ANTE-NATAL CASE

S. N. Garde *

Ballantyne[1], the father of ante-natal care, mentioned the following as the benefits that should be expected from ante-natal care:—

(1) The removal of anxiety and dread from the minds of expectant, parturient and puerperal patients.

(2) The removal of much discomfort amounting in many cases to suffering.

(3) The early and much more satisfactory treatment which can be given to the dangerous complications of pregnancy such as toxaemia; syphilis or heart disease.

(4) The still birth rate will be at once lessened.

(6) One may confidently look for a fall in the maternal death rate, due to such obstetric complications as sepsis, haemorrhage, embolism and the like and to the operative interference they call for.

Ante-natal care if *properly* and conscientiously followed would achieve these benefits.

DIAGNOSIS OF EARLY PREGNANCY

It would not be out of place to discuss briefly the diagnosis of early pregnancy.

Amenorrhoea, morning sickness, frequency of micturition are the earliest symptoms of pregnancy. Breast signs, violet discoloration of the vulva, increased moisture and discoloration of the vagina, softening and discoloration of the cervix, enlargement of the uterus and Hegar's sign, felt bimanually, are the earliest signs of pregnancy. The signs of early pregnancy need not be discussed, except that in the obese and multiparus patients it is indeed difficult to appreciate the slight enlargement of the uterus. The symptoms on the other hand need to be discussed briefly as they might occur without pregnancy.

Amenorrhoea is usually the earliest symptom. Amenorrhoea coming on in a woman of child bearing age, who has been regular before, is highly suggestive of pregnancy. The other possibilities are, a unmarried girl exposed to the risk of pregnancy, a married person who strongly desires a child and cannot get one, mental shock, change of climate and surroundings and rarely general conditions *e. g.* pulmonary tuberculosis.

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Morning sickness: Most pregnant women experience sickness; only a few never have it. Usually it starts by the 6th week and disappears by the 14th. Women who fear pregnancy or greatly desire it, may get morning sickness without being pregnant. Vomiting of course can occur due to associated conditions and they must be always kept in mind.

Frequency of Micturition: In early pregnancy, frequency of micturition may occur due to the exaggeration of the anteflexion of the uterus resulting in irritability of the bladder. Urinary infection also causing day and night frequency must be excluded.

No single sign or symptom mentioned above is diagnostic of early pregnancy. Collectively of course they are very useful in making a diagnosis of early pregnancy. X-Rays before the 16th week are useless. The only reliable way of making a certain diagnosis of early pregnancy is by means of one of the three hormone tests for pregnancy, the Aschheim-Zondek (mouse), the Friedman's (rabbit) or the Hogben (African toad) tests. In places where there are no facilities for doing these tests, three injections of Prostigmin (Roche) dose 1 to 2 c. c. daily will serve as a useful test. If the period does not come after two days of the last injection it is suggestive of pregnancy. This is correct in 60% of cases. Gillifen and Gregg[7] proposed an intradermal test with antiutrin (Parke Davis & Co.—Chorionic gonadotropic hormone). The basis of the test is that the pregnant woman would not be sensitive to the gonadotropic substance found in pregnancy urine. The test is worth trying provided it is realised that the test is unreliable.

EXAMINATION OF THE PATIENT

It must be emphasized that routine ante-natal care begins as soon as the diagnosis of pregnancy is made. It is unfortunately a common, and yet erroneous belief that the ante-natal care begins at the 7th month. Most patients, and even some practitioners believe that the pregnant woman has to go for registration at the 7th month and then for delivery.

The examination must be thorough and orderly. The history is taken first, then a general medical examination, and then obstetrical examination and lastly the investigations.

HISTORY

The history includes the family history, personal history, history of present pregnancy, menstrual history and previous obstetric history in multiparae.

Family History : Enquire regarding the conditions that are likely to affect child bearing, particularly multiple pregnancies, pulmonary tuberculosis, and high blood pressure.

Personal History: Enquire into the history of the patient having suffered from measles, chicken pox, small pox, whooping cough, diphtheria and rickets in childhood, sore throats, heart or kidney diseases, tuberculosis, appendicitis and any operations, in adolescence. Most of these conditions damage the kidneys (toxaemia), others affect labour and a few the puerperium.

Present Pregnancy : Enquire particularly about morning sickness, bleeding (warning hæmorrhage), constipation, breathlessness, sleeplessness, cramps, pain and discharge.

Past Obstetric History : Enquire into how many full time deliveries she had had. Ask for the ages of the oldest child and the youngest. Carefully go into the history of past pregnancies, labours and puerperium. Enquire into the weights of the infants at birth. Take a detailed history of any abortions she has had, particularly the month at which she had the abortion, whether there was any post-abortal sepsis and whether she could ascribe them to any particular cause.

GENERAL MEDICAL EXAMINATION

At the first examination take the height and weight and then go over the various systems. Note the general state of nutrition and the condition of the teeth, tongue and throat. The breasts should be examined and their state of development and the condition of the nipples noted. The mucous membranes are examined for anæmia, the feet and the legs for oedema and deformities (rickets). Note if there is a male distribution of the hair as it might indicate a male type of pelvis.

Weighing : The patient should be weighed at each visit. To be of real value the weighing machine must be accurate and the patient as far as possible wear the same clothes . Cummings[4] who investigated 1000 pregnant women found the total average gain of 25 lbs. during pregnancy, the monthly gains in weight being, 0,1,4,4,5,5,3,3, lbs. It is a good working rule to consider that more than 5 lbs. gain in any month or a sudden gain at any time, is an abnormal increase in weight. And an abnormal increase in weight is often the earliest sign of pre-eclamptic toxaemia.

Blood Pressure: This must be recorded at each visit. A rise of blood pressure is often the earliest sign of toxæmia. Browne[3] considers a systolic pressure above 120 mm of Hg and the diastolic above 80 as raised. Many authorities consider this as an unduly severe standard. To support the correctness of his contention he has quoted the work of Robinson and Brucer[9] and his own vast experience.

Examination of Urine: Routinely the urine is examined for albumin and sugar. If albumin is detected a catheter specimen should be taken to exclude the possibility of contamination from the vaginal discharge. Albuminuria is usually a late sign of pre-eclamptic toxæmia, œdema or raised blood pressure preceding. Rarely it might be the first sign. If sugar is detected, it is most likely to be lactose. To differentiate between glucose and lactose the osazone test is employed. It is however important to take the blood sugar curve and exclude the possibility of diabetes. If there is a suspicion of urinary infection, which is not uncommon, an examination for pus cells will have to be made; more than 5-6 pus cells per field is very suggestive.

ROUTINE OBSTETRICAL EXAMINATION

This includes estimating the probable date of delivery, pelvic mensuration, abdominal palpation and vaginal examination.

Estimating the probable date of delivery. The most reliable way is to calculate from the date of the last menstrual period. Add 7 days to the 1st day of the last period and either count forward 9 months or backwards 3 months. Of course the simplest way is to refer to an obstetric table. In taking the history of the last menstrual period, always ask whether the period was normal. It is not uncommon for a woman to have a scanty period inspite of pregnancy. It is wise therefore to enquire into the last two normal periods to avoid an error in the calculation of the probable date of delivery. An error of 15 days either ways in the expected date of delivery is considered normal. The less reliable methods of estimating the expected date of delivery are based on (1) the fundal height (2) the date of quickening (3) the X-Ray pictures (Roberts or Hastings Ince methods).

Pelvic Mensuration: Bourne and Williams state: "That the external measurements should really be regarded as valueless." Dohrn[7] has well said that the physician who neglects pelvimetry is comparable to one who attempts to treat pulmonary diseases without the aid of auscultation and percussion. I am in entire agreement with this statement. In a primigravida or a multipara with bad obstetric history the following measurements should be taken routinely (1) interspinous (2) intercristal (3) the external conjugate. These measurements give a rough idea of the inlet. It is equally important to measure the transverse diameter of the outlet and palpate the pubic bone and note the pubic arch. To correctly know the type and the capacity of the pelvis, X-Ray pelvimetry is invaluable.

Abdominal Palpation: In the earlier months of pregnancy the abdomen is mainly palpated to see that the fundal height corresponds to the duration of amenorrhoea (pregnancy). It is quite unnecessary prior to the 32nd week of pregnancy to worry about the presentation, still less about the position. It is common for the presentation and the position to vary before this time. If at 32nd week a malpresentation is found we must try and discover the cause. The causes of malpresentation are (1) contracted pelvis (2) placenta praevia (3) twins (4) multiparity (5) hydrammios (6) pelvic tumours.

The commonest malpresentation that one encounters is the Breech. The best time to perform the external cephalic version is 34th to 36th week. It is easier to perform the version at the 34th week than 35th, the dangers being (1) premature rupture of the membranes with onset of labour (2) prolapse and entanglement of the cord (3) separation of the placenta (traumatic accidental haemorrhage) (4) rarely, rupture of the uterus. Fortunately most of the dangers can be avoided by gentle manipulation and avoidance of anaesthesia. Because of the possibility of premature onset of labour some authorities prefer postponing the version to 36th week sc that even if the woman should go into labour the child has a good chance of survival.

The second point is to determine the position, whether anterior or posterior. So far there is no evidence to show that by means of posture or the Buist pads we can change an occipito-posterior position to an anterior. Buist pads do help to change an occipito-lateral to an anterior position. But just these cases need no help as they invariably rotate forward. In addition it must be realised that the Buist pads cause physical discomfort and mental anxiety which more than offsets any possible advantage they may possess.

The last, but not the least, one has to ascertain the relation of presenting part to the brim. In a primigravida the head is normally engaged by the 37th week. If the head is not engaged by this time we must ascertain the reason for it. In 20% of cases no cause can be discovered for the non-engagement. The common causes of non-engagement of the head are (1) contracted pelvis (2) occipito-posterior position (3) placenta praevia (4) multiple pregnancy (5) hydramnios (6) pelvic tumours (7) and a loaded colon.

It is outside the scope of this article to discuss each of these conditions. But it would not be irrelevant to discuss briefly cephalo-pelvic disproportion. To estimate the degree of disproportion is one of the most difficult problems in obstetrics. Radiology does help. Conclusions based purely on radiological findings give a more gloomy picture than is the case. Radiological help, therefore, must supplement our clinical judgment. The method commonly used to estimate the degree of disproportion is Munro-Kerr's modification of Muellers method. For the last 3 years I have been using Chassar Moir's method of estimating disproportion by external manipulation. An assistant is asked to exert pressure on the fundus of the uterus by means of his forearm. The accoucher then grasps the head with his left hand and pushes it downwards and backwards into the pelvis. Then he places the index and the middle fingers of the right hand on the upper border of the symphysis to estimate the degree of overlap. It may be found (1) That the head can be made to enter the pelvis. This means there is no disproportion and the woman would deliver normally or at the worst with forceps (2) that the head over-laps so much that the parietal bone overhangs the anterior surface of the symphysis. Vaginal delivery in such a case is not possible and a caesarean section must be chosen as the treatment.

It is admitted that Chassor Moire's is a crude method of assessing disproportion. However, I have found the method very useful and it certainly has the advantage of simplicity.

Without fear of contradiction it may be stated that premature induction of labour must not be used in the treatment of disproportion in a primigravida. Multigravida, of course, are a different problem. We have the previous obstetric history to guide us. Here in suitable cases premature induction of labour could be usefully employed and a caesarean avoided.

Vaginal Examination : It is always wise to do a vaginal examination at the first visit. The great advantage is we can discover pelvic tumours without symptoms early. If discovered these could be dealt with more conveniently at this early time. Another advantage of an internal examination is that it gives us a better idea of the capacity of the pelvis than what we get from the external measurements.

INVESTIGATIONS

X-Rays : X-Rays are used in cases where there is a doubt about the presentation or there is a suspicion of fœtal abnormalities, for pelvimetry and cephalometry. In some clinics abroad X-Ray pelvimetry is done routinely on all primigravida. It is a good idea. If it is not possible to do it routinely, it should certainly be carried out if the following conditions exist:—(1) short stature (2) evidence of rickets (3) evidence to suggest an android pelvis (4) floating head in a primi-gravida at the 37th week (5) history of previous difficult labours in a multipara or the child dying soon after delivery.

Two views should be taken, an antero-posterior and a lateral. The lateral is the more useful one in cephalo-pelvic disproportion. It also gives a better idea of the outlet. But the antero-posterior gives a better idea of the architecture of the pelvis and of the fœtus. Cephalometry is not developed to the some extent as pelvimetry. It is useful in estimating the extent of cephalopelvic disproportion and in estimating the maturity of the child. It has already been stated that conclusion based solely on radiology tend to be more pessimistic than is the case. Radiology should supplement clinical judgment and not replace it. It is important that the obstetrician and the radiologist should work in co-operation. For fœtal deformities and doubtful presentation a plain antero-posterior X-ray would be best.

Routine Screening of the Chest: A strong plea is made for doing this routinely. The incidence of pulmonary tuberculosis in pregnancy is the same as in general population. The figures for Britain are 1 in 200. Mass radiology has demonstrated that pulmonary tuberculosis can exist without symptoms. The incidence of tuberculosis is much higher in our country. Dr. C. S. Patel[8], considers 1-60 as fair estimate for Bombay Presidency. It can be taken as the figure for the whole country. With such a high incidence it is indeed very desirable to do routine screening of the chest.

Blood Examination: The red blood cells must be counted and hæmoglobin estimated at the first visit. It is particularly important to do this in our country where the incidence of anaemia is so high. Wassermann reaction or the Kahn's test is done routinely. As it is difficult to do so in private practice, it must be done where the history is suggestive, *i.e.*, history of premature labours, macerated fœtus and still births. Syphilis is rarely a cause of abortions.

Vaginal Discharge: Normally in pregnancy there is an increase in the vaginal discharge. If the discharge is profuse, purulent or irritating or if the patient should complain of it, the discharge must be examined microscopically and also by gram staining. The common causes of Leucorrhœa in pregnancy are (1) fungus infection (2) gonorrhoea (3) syphilis. Gonorrhoea should be treated with penicillin and sulphonamides, syphilis with penicillin, arsenicals and bismuth. Fungus which forms the largest group must be treated with application of 2% gentian violet frequently. Apart from the annoyance the discharge causes to the patient, it must be treated because quite often this vaginal discharge causes ophthalmia neonatorum and occasionally thrush.

Frequency of Examination : The patient should be seen every month from the time of the first visit till the 30th week. Every fortnight from the 30th week till the 36th week and then every week until delivery.

ADVICE

Diet : Professor F. J. Browne[3] in his admirable book, ante-natal and post-natal care has discussed this point in great detail. The following is his summary:—(1) Provided the diet has been mixed and generous one no appreciable increase in its quantity is necessary in pregnancy. (2) At least half the protein should come from animal sources, *viz.*, meat, milk and eggs. (3) Care should be taken that sufficient calcium and phosphorus are provided for the proper formation of the foetal skeleton and teeth. The best source of these is milk, of which at least 2 pints should be taken daily. This may include that taken in junkets, custard, etc. Other less important sources of calcium and phosphorus are oatmeal, whole meal bread, fruits, vegetables and green salads. (4) To provide the small quantities of iodine necessary sea fish should be eaten twice weekly. Fish liver oil also contains it in large amounts and is a good substitute if taken daily. (5) The diet should contain a plentiful supply of all vitamins. To ensure this the fresh green vegetables and salads, including lettuce, spinach, cabbage, brussels sprouts or green peas, tomatoes, carrots, potatoes, fresh ripe fruit, and dairy produce eggs, milk, butter and cheese should be eaten daily. Liver should be eaten once weekly. (6) Because of the prevalence of rickets and dental carries vitamin D is probably by far the most important of all the vitamins in pregnancy and lactation, for it is needed to ensure the utilisation of calcium and phosphorus, and their deposition in the developing bones and teeth of the fœtus. Its distribution in food stuffs is very limited for only egg yolk contains any considerable amount of it. It is advisable, therefore, to give 2 tea-spoonfulls of cod-liver oil, or an equivalent quantity of halibut liver oil, daily. (7) The diet should contain sufficient roughage to prevent constipation. In addition to that in fruit, vegetables and meat, whole-meal bread and oatmeal porridge (eaten with milk at breakfast) are useful and effective.

Dietary Supplements : The People's League of Health and the Toronto experiments have amply proved the value of dietary supplements. The demands of all the vitamins are increased in pregnancy. There are numerous proprietary multivitamin preparations on the market. Any one of these preparations must be given throughout the pregnancy and puerperium. In prescribing a multi-vitamin preparation, one with

9000. (I.U) of A and 340 (I.U) of D is suitable. Iron is best administered as a ferrous salt. The dose will largely depend on the percentage of haemoglobin. Iron is better tolerated when taken with milk than with water. Taking iron with milk is particularly advised for those patients who cannot tolerate it. Calcium (1-2gms) should be given throughout the pregnancy. It could be profitably stopped in the last 3 weeks of pregnancy.

Care of the Breast: Breasts must be prepared for sucking. If nipples are retracted an effort must be made to draw them out by rolling them between the thumb and the fingers. The nipples should be kept clean by daily washing them with soap and water. The patient should be instructed to apply cold cream and Eau de Cologne to the nipples once a month. She should be advised against compressing the breasts. If the breasts are pendulous a comfortable support should be advised.

Marital Intercourse: Marital intercourse should be completely avoided in the last 3 months of pregnancy. There is reason to believe that there is higher incidence of puerperal infection amongst women who have intercourse in the last 3 months. There is also room for suspicion that it might lead to premature rupture of the membranes with onset of labour. If there is history of abortions it should be forbidden throughout the entire pregnancy.

Exercise: Walks in the open air are the best forms of exercise. It is difficult to standardise how long the patient should walk. That depends on each individual. The golden rule is to stop short of fatigue. There is no reason to stop the household duties. These can be carried on till the end of pregnancy. But if the patient is doing hard manual work such as working in mills, she should stop working at least 6 weeks before term. All violent exercises should be avoided during the last 6 months but if there is history of previous abortions they are best avoided from the beginning.

Sleep: The pregnant woman should have at least 8 hours sleep every night. It is also desirable to have a couple of hours rest in the afternoon. As far as possible it is best to avoid drugs. Natural means like walks in the open air, a bath at night or a cup of Horlicks or ovaltine would help much in inducing sleep.

Constipation: This is quite common during pregnancy. It is probably due to the action of Progestin on the involuntary muscle of the intestines and the pressure as a result of growing uterus. As far as possible it should be treated by the use of proper diet and exercise. Many cases, however, require the aid of drugs. Strong purgatives should be avoided. The best drugs to use are phenolthalein, milk of magnesia, cascara and senna. Liquid paraffin should be avoided on the theoretical grounds that it might deprive the patient of fat soluble vitamins by dissolving them.

Travelling: Much will depend upon the comfort with which one can travel. It is difficult to make general statements. Each case must be judged individually. If there is history of abortions it is best to avoid long or uncomfortable journies. In any case it is best to avoid travelling in the last four weeks of pregnancy. Sea and air travel definitely carry more risk than land. Apart from the danger of miscarriage or premature onset of labour, it is good to keep in mind the akwardness of the situation in case the delivery should occur during the journey.

The Teeth: Ideally every pregnant woman should see her Dentist at least twice. Elective dental work should be postponed till after the delivery. But there is no reason at all to postpone urgent work.

Re-Assurance:—A good obstetrician must spare all the time that is required to allay the numerous anxieties the patients manage to collect. The doctor must encourage the patient to come to him for the problems that confront them, instead of getting them solved by their relatives and friends. The patient must be made to feel that no problem she has, is frivolous or ridiculous. At each visit it is good to tell the patient that all is well. Small explanations about the various examinations the doctor does are always welcome by the patient. If during routine examination some abnormality is discovered it is wise not to tell the patient but to inform some responsible member of the family. It is important that when the woman goes into labour she is fit both physically and psychologically. A doctor seriously interested in obstetrics will learn much from Dr. Grantley Dick Read's[5] book "Natural child-birth". He has made many useful suggestions as regards the psychological bringing up of the pregnant woman.

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CURRENT MEDICAL LITERATURE

MEDICINE

RESPONSE OF TROPICAL SPRUE TO VITAMIN B 12. SPICS, T. D. AND SUAREZ. R. M. BLOOD **3**: 1213-1220, 1948. 5 fig. 9 ret.

The authors have treated five cases of tropical sprue in Puerto Rico with Vitamin B 12. These patients had the following criteria (1) macrocytic anaemia as determined by Wintrobe's Indices (2) megaloblasts in the bone marrow (3) the erythrocytic count below 2.5 millions per cmm. (4) the patients were untreated (5) low reticulocytic count before treatment. The patients were kept on sprue diets used by the authors. There was general clinical and hœmatological improvement to a dose of 10. 20 or 25 microgrammes. There was no improvement in a case treated with 4 microgrammes. If the dose was not large the patient tended to relapse clinically and hœmatologically. In the authors' opinion—"This therapeutic compound, per unit of weight is more effective in treating human disease than any compound that yet has been used."

J. C. PATEL.

THYMIDINE AND VITAMIN 12 IN PERNICIOUS ANAEMIA. UNGLEY, C. C. Lancet **1**: 164-165, 1949. 8 ref.

Thymidine is a substance which would replace vitamin B 12 in the nutrition of certain Lactobacilli. This microbiological evidence suggested a trial of thymidine in a case of pernicious anæmia. 48 mg. of thymidine was given to a patient with pernicious anæmia without any response. Later this patient responded adequately to 7.5 mg. of crystalline vitamin B 12 of Lester Smith. It is concluded that even though thymidine can replace vitamin B 12 in the nutrition of certain bacteria it has proved ineffective in pernicious anæmia.

J. C. PATEL.

CRYSTALLINE ANTI-PERNICIOUS ANAEMIA FACTOR IN TREATMENT OF TWO CASES OF TROPICAL MACROCYTIC ANAEMIA. J. C. PATEL, BRIT. MED. JOUR. **2**: 934-936, 1948. 2 tables, 11 ref.

Lester Smith's crystalline red pigment material was given to two cases of macrocytic anaemia with megaloblastic marrow. A single dose of 80 microgrammes was given to each patient. The response in both cases was optimum. The marrow was examined on the day following reticulocytic crisis and it had changed to normoblastic picture.

J. C. PATEL.

VITAMIN B 12, Editorial. Lancet **1**: 151-152, 1949.

This editorial reviews the work done during the nine months since the publication of the work of Lester Smith in England and Rickes and Co-workers in the U. S. A. The number of reports are not many as the supplies of the material is scanty. 250 mg. of crystalline substance is available from one ton of fresh liver. Even though the yield from the liver is small, the effective dose is still smaller. A few microgrammes suffice to produce a reticulocyte response and start the marrow on its change from megalablostic to normoblastic erythropoiesis. Vitamin B 12 contains 4% Cobalt and each molecule has weight of about 1500. It is effective in pernicious anæmia, nutritional megaloblastic anæmia, sprue and few other rare diseases.

A single dose of 6-15 mg. is effective. Spies thinks that 100 mg. is the minimum dosage for producing remission. The Vitamin B 12 is effective in the treatment of subacute combined degeneration. Some workers think that 1 mg. of Vitamin B 12 is equivalent to about 1 U. S. P. unit of Liver extract. American workers have checked the Vitamin B 12 content in the liver extract by the growth of Lactobacillus Lactis Dorner. This raises the hope that if commercial liver extracts owe their antianæmic activity to vitamin B 12 it might be possible to assess their potency by a similar microbiological test. Rickes and his team have isolated from broth cultures of *Steptomycess griseus*, a red crystalline material with all the properties of Vitamin B 12 including cobalt and phosphorus and ability to produce clinical response in pernicious anæmia. The Editorial hopes that it (Vitamin B 12) will be synthesised and prepared at an economic price, perhaps from some source other than liver. If it reproduces all the properties of potent liver extract, then no microbiological assay or clinical testing will be necessary.

J. C. PATEL.

DEXTRAN AS A PLASMA SUBSTITUTE. GUNNER THORSEN, Lancet 1: 132-134, 1949. 5 fig. 8 ref.

Dextran is polydsperoid glycose. polymer dextran with a molecular weight conforming to that of albumin. It is given in a 6% solution with 0.9% of sodium chloride added to it, Dextran is virus free. does not lead to formation of antigens and contains almost no nitrogen. It is nontoxic, it does not injure tissues locally or systemtically. In Sweden, Dextran has been given to 5,000 patients in 20,000 infusions. As much as 4 litres have been given to a patient in a single infusion. The largest amount given to a single patient has been 10 litres. Dextran is used as routine in treatment of shock and for prevention of shock during major operations. Dextran is extracted by kidney in course of 8 days without any signs of renal injury. It is metabolised in the body. It is recommended as a very useful substitute for blood and plasma in cases where increase in blood volume or in colloid osmotic pressure is desired.

J. C. PATEL.

DEXTRAN AS A PLASMA SUBSTITUTE. BULL, J. P., RICKELLS, C., SQUIRE, J. R.. MAYCOCK, W., SPOONER, S. I. L., MOLLISON, P. L., AND PATERSON, J. C. S. Lancet I: 134. 1949.

Dextrans are produced by the growth in culture of various microorganisms, in particular of the non-pathogenic coccus *Leuconostoe meseteroides* in a substract of glucose and phosphate. The substance prepared as above is purified and its molecular size is reduced to that equivalent of albumin by acid hydrolysis.

The infusion of large volumes of dextran in cases of very severe burns demonstrated its adequacy for volume replacement and for the maintenance of osmotic pressure. Dextran appeared to possess the positive qualities required of a plasma substitute. Its fate in human body is unknown. Evidence suggests that dextran gradually dis appears from the body but a definite statement cannot be made until further experiments have been made to show whether its disappearance is complete. It was useful in the same way in cases of surgical shock or hæmorrhage.

J. C. PATEL.

SPLENECTOMY IN KALA AZAR. MORTON, T. C AND COOKE, J. N. C. Lancet **1**: 920-923, 1949. 2 fig. 12 ref.

Splenectomy has come to be regarded as entirely contra-indicated in the treatment of Kala-Azar since the introduction of Pentamide and potent pentavalent preparations of antimony. The authors review the literature of splenectomy in cases of Kala-Azar and advocates it in cases of Kala-Azar where the disease has become resistant to antinomy and pentamidine. They report three cases of Kala-Azar which were drug resistant and were treated successfully with splenectomy. They advocate further treatment with antimony or pentamidine following splenectomy.

J. C. PATEL.

SURGERY

INTRA-PELVIC OBTURATOR NEURECTOMY FOR RELIEF OF CHRONIC ARTHRITIS OF THE HIP—KEY, J. A., AND REYNOLDS, F. C, SURGERY, **24**: 959-967, Dec. 1948.

When the surgeon realises that the hip is permanently damaged and that no form of treatment can be expected to restore the joint to normal, he must decide whether to treat the hip conservatively or operatively. Conservative treatment fails to afford relief. The patient rebels against the enforced rest and wishes for something active. Manipulation and plastering rarely result in satisfactory improvement. Only operative treatment has to be considered. But in many of these old and chronically painful hips, the operation may prove formidable and usually entails a long post-operative convalescence, especially after arthrodesis. The authors have not had satisfactory results with arthroplasty, even with the Smith-Petersen vitallium mold technic. Other methods like cheilotomy and acetabuloplasty have given success in only a minority of patients.

The authors have found that section of the obturator nerve in these cases is a simple operation that gives satisfactory relief from painful disability. The approach is through a 5-inch incision along the lateral border of the rectus, and extraperitoneal exposure of the obturator nerve.

They have performed the operation on 18 patients; included in these were 7 patients with malum coxae senilis, 2 with traumatic arthritis following fracture, 2 with old slipped epiphyses, 3 with old pyogenic infection of the hip, and some others. The results were as follows: In 16 patients there was considerable relief, in most of them so great as to enable them to express gratitude for the operation. In 9 of these the relief was 100%. How much of this relief is due to the weakening or paralysis of the adductor muscles of the thigh, which are usually in a contracted state, is not known. From their experience the authors believe that the best results are likely to occur in cases in whom there is adductor spasm or contracture.

E. J. BORGES.

THE SIGNIFICANCE OF THE SO-CALLED REACTION OF DECOMPRESSION IN CHRONIC RETENTION OF URINE—ARNE HOMB, ACTA CHIR. SCANDINAV. **96** : 297, 1948.

Although the accepted teaching has been that sudden decompression of a chronic retention of urine in prostatic patients is often followed by reactions like hæmorrhage, and anuria, in 1919 Ingebritsen at Oslo began to perform immediate cystostomy on such patients because of bad results he had with slow decompression.

The present author reviews 160 cases of prostatic retention in whom cystostomy was done within 2 or 3 days of admission, a catheter having been passed only to relieve the patient and determine the residual urine. In 58 patients with blood urea values above 50 mgs. per cent and residual urine of over 400 cc, an immediate cystostomy was done without any preliminary catheterisation. There were only 2 deaths in very feeble men in this group. Cystostomy was followed by diuresis and a drop in blood urea content in all but 2 cases. Only one "reaction" occurred in the form of a rise in blood urea, but this was transitory. The author is convinced that rapid decompression if accompanied by forcing fluids is not dangerous.

E. J. BORGES.

PEDIATRICS

SCIENTIFIC CONSTRUCTION OF THE NORMAL CHILD'S DIETS. BROWN, A. Lancet (1948) 2: 877-881, 1948. 29 ref.

Prof. Brown of Toronto University in a lecture at Birmingham (England) reiterates his belief in proper supervision of child's nutrition as a means of maintaining good health. He had observed that the infant during its first six months of life is greatly affected by the mother's diet during the prenatal period. Children of those mothers who were given supplementary feeds developed fewer and less severe complications. The provision of an adequate food-supply for the child even before birth is therefore very important. Prof. Brown is convinced that breast-milk produced by a healthy mother is the best of all foods inspite of all advances in artificial feeding. The self demand schedule in breast-feeding is an interesting new development. It throws less strain on the mother. The rigid schedules are becoming less common. It is better to feed a hungry child an hour or so before the feeding time than to allow the child to exhaust itself by crying or to allow the child to sleep longer if the child is contented. The "full" baby is a stupid little animal; the hungry one is smart and intelligent looking and is easily roused. The child which cries at night is usually hungry probably because the mother has less milk by the evening. Rickets is commoner than imagined and he suggests Codliver oil from the age of two weeks till 2 years. Dental carries is much more prevalent in those who receive less vitamin D than their daily requirement in their diet. Infantile scurvy is not common. Fresh orange juice has better antiscorbutic properties than synthetic ascorbic acid. Cereals contain vitamin B complex and should be given early in life.

J. C. PATEL.

STATURAL DISTURBANCES IN PEDIATRIC PRACTICE. I. P. BRONSTEIM AND S. P. DITKOWSKY—Med. Cl. of N. America, Jan. 151-160, 1948.

The statural disturbances in children may be either an under-or over-growth. Besides genetic, endocrinal and systemic disturbances, caloric under-feeding may arrest growth. It is suggested that in these children the pituitary slows down its activity. Though infants with feeding difficulties suffer in their growth, yet in children seen at a later age for stunted growth food is not an etiological factor. Some children who grew normally for some time may slow down after an acute illness at first because of loss of appetite and later on inspite of improvement in appetite. This may be due to inadequacy of anabolic hormone.

Thyroid deficiency causes dwarfism. In these dwarfs there is muscular hypertrophy besides the usually well-accepted signs and symptoms. Thyroid deficiency as cause of understature in the adolescent period may be missed. Basal metabolic rate though a valuable test is not specific. Adequacy of dose of thyroid in these cases is determined by the physical, osseous and mental growth.

The diagnosis of pituitary dwarfsin is made by exclusion. The evidence for intra- or extra sellar tumours is rare. The diagnostic points are understature, symmetrical proportions, sexual infantilism, delayed epiphyseal closure, history of natural growth. Preparations of the anterior lobe of the pituitary have not been useful. Better results are obtained with chorionic gonadotropins in male children and gonadal substances in male and female children.

Androgens given intermitently may promote spurts of growth. In adolescent girls ovarian agenesis is a cause of dwarfism. Progeria, is a rare condition characterised by dwarfism, precocious senility and bony retardation with premature epiphyseal fusion.

Increased stature may be a normal variation being racial or familial. Other causes are prepubertal hyperpituitarism, precocious puberty and hypergonadism. Growth may be inhibited by the use of antagonistic hormones. The authors were able to stop sexual and statural growth by the administration of 100,000 units of follicular hormone.

G. COELHO.

EPILEPSY IN CHILDHOOD. M. G. PETERMAN. J. A. M. A. **138**: 1012-1019, 1948. 21 figs., 48 ref.

The author discusses the newer methods of diagnosis and treatment of this condition. "The most reliable and positive means for making a diagnosis of epilepsy is an adequate and complete history together with a description of the seizure". But this must whenever possible be confirmed by electrogram. This is particularly needed in cases of fainting spells, behaviour problems, and fever convulsions. But a typical electrogram is not often found in children before six years of age.

In the treatment of petit mal tri-methadione will control about one third of the cases of uncomplicated petit mal. But the drug may precipitate grand mal attacks and has a depressing effect on the bone-marrow. Paradione has been introduced for the treatment of those patients who have not responded to trimethadione.

Both these drugs must be supplemented with phenobarbital. The author tried thyphenytion on 9 patients with petit mal, 7 of whom improved. The dose varied from 0.13 g. to 0.39 g. In the treatment of grand mal in children diphenylhydantoin sodium has not been such a success. According to Peterman it is a "useful addition to the list of anti-convulsants" and "phenobarbital remains the most effective and satisfactory drug available for the treatment of major convulsions." Peterman treated over 100 convulsive patients with a new barbiturate AN[23]. Of these 21 had grand mal: amongst these 14 have improved. In his experience phenobarbital has been superior to "dilantin" and mesantoin.

G COELHO.

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2. White, J. C., and Smithwick, R. H.: The Autonomic Nervous System, pp. 271, New York, the Macmillan Company, 1941.

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MEIGS'S SYNDROME

Hira B. Patil *

INTRODUCTION

The presence of a pelvic tumour associated with ascites and pleural effusion had been regarded immediately suggestive of an inoperable malignant tumour before 1937 when Meigs and Cass[16] described 7 cases illustrative of this triad as a syndrome occurring in cases of benign tumours of the ovary and stressed its curability by surgical removal.

The syndrome is not quite so rare as it seems. There is little doubt that often it is missed. The important aspect of the question is that the removal of the ovarian tumour is curative though clinically the case may resemble one of a malignant growth because of the physical signs and the symptoms which it produces. From the physician's point of view, a knowledge of this syndrome is of value as otherwise it may happen that the patient is subjected to repeated aspirations without any lasting benefit, and is doomed to a slow death. On the other hand some patients have been cured having received proper and timely operative treatment.

As an example may be cited the case described by Simon[21]. The patient was 55 years old, had a large femoral hernia with a discharging ulcer on its most dependent part. The chest had revealed physical signs of fluid on the right side and there were signs of ascites. The abdomen was noted to be filled with a hard smooth freely moveable mass which seemed to spring from the pelvis. Her general condition was very poor. To quote from his paper "the patient was seen by all members of the visiting staff, one or two of whom urged delay believing that operation could only result in a fatality. It was suggested that the pathology would soon be revealed at autopsy. This conclusion was, in spite of the fact that Meigs's syndrome was considered by all as a possible diagnosis." 2,500 c.c. of clear yellow fluid were removed from her right chest and the next day she was operated on. On opening the abdomen 500 to 750 c.c. of clear straw coloured fluid escaped. A rapid right salpingo-oophorectomy was done. The ovarian tumour removed was about 27 cm. in diameter and weighed 5,200 grammes. The pathological diagnosis of the tumour was fibroma of the ovary. Recovery was rapid. After three months the femoral hernia had disappeared though an impulse on coughing persisted. The patient had by then gained 25 lbs. in weight and returned to work. Eighteen months after the operation she was still well. This is given by Simon[21] as a classic case of Meigs's syndrome and he puts forth the thesis that one must operate when operation is the sole hope. The patient referred to above was dying because of the ascites and a constant loss of protein bearing fluid and the actual physical inability to take in an adequate amount of food because of the tumour.

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Borg[2] reported a case of this syndrome which came under his observation. The patient aged 44 had all the physical signs and symptoms of this syndrome for six months. Aspiration of the right pleural and peritoneal fluid had been done, the former twice. The fluids had shown the usual characters of a transudate. Meigs's syndrome had been diagnosed and the patient was being handed over to the gynæcologist for operation, when she collapsed rather suddenly and died. A post-mortem examination revealed the following: massive hydrothorax of the right side and collapse of the lung, a small hydrothorax of the left side, a fair degree of ascites, tumours of both the ovaries which on naked eye and microscopic examination were found to be fibromas; the tumour of the right ovary was huge and the one of the left was small. This is a good illustrative case of the unfortunate results of delay.

Simon[21] suggests that both ascites and hydrothorax probably appear only after the ovarian tumour has been present for some time. In other words almost all cases of Meigs's syndrome might be classified as "neglected or . . . unexamined patients." It is because vaginal examinations are more common today that one does not see many more cases in this category. The possibility of missing fluid in the chest has also to be considered. An amount like 1,000 or 1,500 c.c. of fluid in the chest cavity may not necessarily produce symptoms. A thorough physical examination or a chest X-ray would be necessary to establish its presence.

HISTORY

The earliest authentic case appears to be the one described by Cullingworth[4] of Manchester in 1879. MacFee[11] refers to this case. Cullingworth's patient, a widow aged 36, was first seen for uterine hæmorrhage of three months duration and was apparently in good health. In about three months the hæmorrhage had stopped but from that time onwards her health had rapidly declined. "She had lost flesh and ascites had supervened." She had suffered from "pleurisy first on the left side and subsequently on the right." About three months later she is described to have become suddenly worse with symptoms of intense dyspnœa and general collapse and died. Autopsy revealed the following "the left pleural cavity was . . . full of fluid, . . .the left lung was entirely collapsed. . . .There was a large quantity of fluid in the peritoneal cavity and the peritoneum was thickened and opaque. Large bilateral solid tumours of the ovaries were found." After microscopic examination the diagnosis of ovarian fibromata was made.

In his paper MacFee[11] refers to the interesting discussion said to have occurred on Cullingworth's tumour case in 1879. MacFee concludes. "...it appears probable that this case was one of benign ovarian fibromata associated with peritoneal and pleural effusion. It is also likely that this is one of the first, if not the first, to appear in the modern literature."

If, describing cases of this triad in a chronological order is of value, from the point of view of the history of the condition, the second case can be said to be the one of Lawson Tait, studied and operated on in 1890-1891.

Meigs *et al.*[15] in their paper include an abbreviated account of Lawson Tait's discussion on his case. Readers are invited to refer to the original account by Tait[22], McIlrath[12], and Meigs *et al.* The important observation by Tait was "the opening of the abdomen has very little risk, if any, greater than the process of tapping, which has to be employed for the purpose of giving the patient relief." Speaking of laparotomy Lawson Tait observed " . . .but if one of the lives had been saved by the discovery of the mistake I think it would have been quite justified in performance of the incision in all the rest of the cases." Lawson Tait therefore can be said to be the first one recommending laparotomy for patients with abdominal and chest fluid for, he considered that, that combination did not always mean cancer.

Briefly, Lawson Tait's patient was aged 36, had effusion in the peritoneum and pleura; she had been tapped repeatedly and was finally operated on. An ovarian tumour weighing 2 lbs. 2 ozs. had been removed. Microscopically it was a fibroma. The patient had finally recovered.

Though it was Tait who brought the triad of symptoms of abdominal tumour, ascites and hydrothorax with emaciation and weakness first to the notice of the medical profession in 1892 and stressed the advisability of an exploratory laparotomy on every case of such type, it was Rhoads and Terrell[18] who first used the term Meigs's syndrome while reporting a case in 1937. Thereafter reports of cases of Meigs's syndrome have appeared in the medical literature. Isolated cases from old accounts have been tabulated by several authors. After the year 1934 the syndrome appears to have been noticed with greater frequency and four to five cases have appeared in the literature every year. Simon[21] gives the total as 44 up to June, 1947.

Gardiner and Lloyd-Hart[6] give a brief review of cases of Meigs's syndrome. These authors also state that the first case was of Cullingworth 1879, and the second was of Lawson Tait 1892. In their opinion the third case was of Borg[2] 1941, the fourth of Gild[7] 1943 and the fifth and sixth of Clay *et al.*[3] The above may be considered as a sequence of cases of Meigs's syndrome in the British literature.

Gardiner and Lloyd-Hart[6] writing in 1944 in the *Lancet* state "...the condition little known in Britain, deserves wide recognition because the patient may come first under the care of either physician or surgeon depending on her presenting symptoms, and though the condition responds completely to surgical treatment he may well regard it as malignant and inoperable if he is unfamiliar with it..."

Similar have been the remarks by several authors in recent years. Gardiner and Lloyd-Hart[6] give an account of a case in which the ovarian tumour "turned out to be a fibromyxoma with no evidence of malignancy." About the same time, Clay *et al.*[3] give an account of two interesting clinical cases of this syndrome occurring in England.

From the above account it will be evident that Meigs's syndrome has come into its own only recently. No reference to published cases in India have come to the notice of the author.

There is therefore some justification to discuss the several features of this syndrome.

INCIDENCE

In describing the incidence of Meigs's syndrome reference to several aspects will be more appropriate— 1. Incidence of fibroma of the ovary, 2. Association of the ovarian fibroma and ascites, 3. Association of ascites and ovarian tumours benign and malignant, benign tumours in particular, and 4. Co-existence of hydrothorax, ascites and fibromas with other types of benign tumours of the ovary.

The incidence of an ovarian fibroma has been variously reported as ranging between 2 and 4 per cent. Hoon[8]; Rhoads and Terrell[18], Bomze and Kirshbaum[1] from their own material state that fibromas make up 7.7% of all ovarian tumours or 9.9% of the benign group. Dockerty and Masson[5] found ovarian fibroma as "the second commonest of the solid ovarian neoplasms," which "accounted for 5% of all ovarian tumours surgically removed at the Mayo clinic."

The occurrence of ascites with ovarian fibromata is very inconstant. Owen[17] refers to the following data:—One in seven cases collected by Fairbairn, in five out of eleven cases by Doran and in only 5% of fibromas, those which are "diffuse," by Hellman. Meigs and Cass[16] in their review of the literature record that various authors report that 13.7 to 40 per cent. of the ovarian fibromas are accompanied by ascites.

The occurrence of the triad is rarer still. Dockerty and Masson[5] report 2 cases having hydrothorax in the 51 cases of ascites in 283 cases of ovarian fibromas. Rubin *et al.*[20] give the following figures from the study of two series. In a total of 23 tumours, 9 had ascites and only 1 had hydrothorax. In the second series in a total of 55 benign tumours of ovaries, hydrothorax was noted in 1 only. In this group the authors include 23 theca-cell tumours, 2 papillary fibroadenomas, besides, 30 as the mixed group of fibromas and fibromyomas. In this latter group ascites was noted in two and hydrothorax in none. In the 23 theca-cell tumours ascites was noted in seven and hydrothorax in one. It is not possible to deduce with any accuracy the actual incidence of the triad, hydrothorax, ascites and the ovarian tumour, though it is true that a fair number of cases under the title, Meigs's syndrome have been reported. The question as regards the type of the ovarian tumour to be included in the triad is a subject worth discussing and will be referred to in a subsequent part of this papar.

A few facts relating to the clinical features of the syndrome may be summarised here.

AGE

The condition may occur at any age after maturity but is most often discovered in the early post-menopausal period. Majority of the cases however are reported between 36 and 64 years. Rubin *et al.*[20] record the youngest case at 16 and oldest at 76. It is stated that no cases are observed in the pre-pubertal age group.

SYMPTOMS

The presenting symptoms may be referable to the chest—dyspnœa, pain, discomfort in the chest; and to the abdomen—enlargement and consequent discomfort and pressure symptoms. There may be cachexia and effects of dehydration from repeated tapping of the chest and the abdomen.

Less often the symptoms are referable to the abdomen alone or to the chest alone. Slight continuous uterine hæmorrhage, menorrhagia, normal menstruation and amenorrhœa have all been reported,—amenorrhœa being the commonest condition. Average period of the presence of the tumour has been 33 months with extremes of one week and 30 years. Pain was the principal complaint in a considerable number of patients, but the pain when present had no diagnostic feature (Dockerty and Masson[5]). None of the cases had rise of temperature above 99.8°F.

PHYSICAL SIGNS

The usual physical signs relating to hydrothorax and ascites were present and in nearly all cases the tumour could be palpated easily either without paracentesis or after it. The size of the tumour varied considerably. Sometimes it was larger than an adult's head, rarely the tumours weighed more than 2,500-3,000 grammes, Simon[21]. Bomze *et al.*[1] reported a tumour weighing over 7,000 grammes. This was removed at autopsy. MacFee[11] reported an ovarian tumour in a case of Meigs's syndrome. The tumour was multilocular cyst-adenoma. It measured 27 × 30 × 14 cm. and weighed 17 lbs.

The occurrence of the fibroma may be noted in relation to one or both the ovaries. The average size, unilateral or bilateral, representing a clinical threshold for the production of symptoms was one with a diameter of 6 cms. (Dockerty *et al.*[5]).

The hydrothorax is commonly purely right-sided, often bilateral and rarely only left-sided. The side of the hydrothorax does not appear to be related to the side of the ovarian tumour. All combinations have occurred.

Cachexia is often present in cases with a long history, and œdema of the feet has been noted in some cases. Gardiner and Lloyd Hart[6] report a case with synovitis of the right knee, with no other obvious cause for it, followed by shortness of breath heralding the onset of hydrothorax and subsequent disappearance of the effusion in the knee; this makes it likely that it was a part of the syndrome.

THE OVARIAN TUMOUR

Dockerty and Masson[5] found uterine fibromas as the most common associated tumours with fibromas of the ovaries. The ovary in which a fibroma was situated was at times simultaneously the seat of simple cysts, dermoid cyst, cyst-adenoma, etc.

The specimens of the ovarian fibromas usually consisted of encapsulated and somewhat irregular masses varying in size from very small to very large sizes like 26 × 23 × 17 cm. The consistency of these tumours has been hard and the cut surface has shown white interlacing bundles of fibres on a greyish background. In some, cysts of varying sizes were seen. In some small subcapsular hæmorrhagic areas were noticed. Microscopically—the average tumour showed a uniform appearance. The cells were small with spindle shaped nuclei arranged partly in parallel bundles and partly in interlacing patterns. The intercellular substance was scarce. Reference to other benign ovarian tumours will be made later.

ASCITES AND HYDROTHORAX

Without going into any detailed discussion of the many theories that have been put forward to account for the more frequent ascites and the less common hydrothorax associated with fibromas and other benign tumours of the ovary, below are listed the main suggestions :

1. Torsion of the pedicle of the tumour leads to outpouring of the ascitic fluid.
2. The fluid is a result of hypoproteinæmia.
3. The pleural and ascitic fluid is due to congestive cardiac failure,
4. There is mechanical obstruction of the venous or lymphatic outflow of the thorax or the fluid enters the pleural cavity *via* diaphragmatic lymphatics,
5. Small congenital openings in the diaphragm allow direct passage of fluid from the abdomen to the thorax, and
6. It is an example of Selye's " alarm reaction."

Gardiner and Lloyd-Hart[6] refer to these in a greater detail and also give some references relating to this question.

Many writers on Meigs's syndrome have discussed the subject without offering any satisfactory explanation of the phenomenon.

THE OVARIAN TUMOUR IN THE TRIAD

It may be useful to survey briefly the views held by a certain number of authors as to the admissibility of different types of tumours of the ovary under the title Meigs's syndrome as a distinct condition. Rhoads and Terrell[18] used the words (" Meigs's Syndrome ") at the end of the title of their paper. The title begins with the words " ovarian fibroma " and consequently it may be thought that the fibroma was the only ovarian tumour consistent with the syndrome. Closer examination of this situation is definitely indicated. Simon[21] states that " the term Meigs's Syndrome should be reserved for those cases which present a solid ovarian tumour associated with ascites and hydrothorax." Simon wrote this in June 1947. Going back for a moment to the publication of Meigs and Cass[16] the following lines are likely to throw much light on the conception of those authors. " All tumours were fibromas or fibromyomas of a diffuse type . . . Such tumours are described as arising from the stroma, the corpus luteum, corpus albicans, the theca interna or externa, the tunica, organised blood clots and even from the walls of the blood vessels. It is most probable however that such tumours arise from the connective tissue stroma of the ovary. In three instances the tumour was called a fibromyoma . . . and without differential staining not done in these cases it is very difficult to state whether the tumour is a fibroma or a myoma. From the description of the tumours as given in the pathological reports, all were of the same type, *i.e.*, large, smooth, and lobulated." This quotation though lengthy enables one to conclude that the oft quoted original authors did not probably mean that a fibroma alone was included in the triad.

Cases have been reported wherein hydrothorax and ascites have been associated with benign ovarian neoplasms other than fibromata, as also with tumours of the uterus. All have responded completely to the removal of the tumours. These include among others: (1) Myoma of the uterus, Kelly and Cullen[10]; (2) Theca Cell tumour, Rubin *et al.*[20]; (3) Multilocular cyst-adenoma, MacFee[11]; (4) Brenner's tumour, Keleman[9]; (5) Fibromyxoma, Gardiner and Lloyd-Hart[6].

Rubin *et al.*[20] even suggest that some of the fibromas mentioned in the literature prior to 1932 may have been theca-cell tumours. To the list of the benign tumours may be added a sixth one,—granulosa cell tumour reported by Vogt[23].

In spite of these facts appearing in the literature it will still be worth discussing more critically the necessity for a stricter definition of the term " Meigs's Syndrome." It will be advantageous in many ways. Meigs meant it to include—benign tumours of the ovary—Simon suggested that all solid benign tumours be included—Rhoads and Terrell put on the title of their paper (fibroma), though many cases cited and reported in literature are not all of fibromas. Taking a broader definition may be risky or even inaccurate.

An account of a recent case, the operated specimen from which was received by the author for a pathological report from a clinical case of Meigs's Syndrome (?) is given below.

The patient aged, 25, multiparous, was admitted into the Lady Hardinge Medical College Hospital, New Delhi, under the case of Dr. Miss D. M. Satur, the gynæcological surgeon. The clinical synopsis of the case briefly is as follows: Gradual enlargement of the abdomen for four months, constipation, difficulty in micturition, anorexia, and pain all over the body. Menstrual history—2-3/30 regular, painless, scanty. Obstetric history—five full term children. On admission to hospital the patient was very weak, pale and emaciated. Significant laboratory findings—Hæmoglobin 50 per cent., R.B.C. 2.9 millions, W.B.C. 6,300 and the blood picture of a hypochromic microcytic anæmia. Clinical examination of the patient further revealed,—heart, lungs normal, right-sided hydrothorax, enlarged abdomen, free fluid in the peritoneal cavity, a moveable hard nodular mass could be ballotted on the left side in the lower abdomen. On P. V. examination a hard irregular mass was felt in the left and the posterior fornix, the right fornix was clear. Provisional clinical diagnosis—of ? malignant ovarian tumour with ascites, ? Meigs's syndrome was made in the first instance.

X-ray before operation (Fig. 1) showed the diaphragm raised on both sides due to fluid in the abdomen and effusion into the right pleural cavity, the level being the third rib at the periphery.

The abdomen was tapped before opening the peritoneal cavity, 18 pints of "clear blood stained fluid" was removed. On opening the peritoneal cavity a hard irregular nodular tumour involving the left ovary and similar but a smaller tumour involving the whole of the right ovary came into view and were removed. The tumours were removed with the uterus—a total hysterectomy was done. Subsequent to the operation the patient recovered completely. X-ray three weeks after operation (Fig. 2) showed the height of the diaphragm on the right side at the level of the anterior end of the fourth rib. The effusion on the right side had cleared up. The phrenico-costal angle was clear. Both the X-rays were by Dr. Mrs. R. Kolhi, Radiologist.

Pathological report (Fig. 3)—the left ovary was occupied by a tumour 15×11×10 cm. which was encapsulated and somewhat nodular. On the cut surface the greater portion of the tumour presented a whitish firm felt work with areas of necrosis scattered through it. In the lower portion about less than a fourth of it was soft and hæmorrhagic. The other ovary was also occupied by a growth which was much smaller—6.3×5.7×4 cm. It was firmer and very hard to cut. The cut surface showed three different types of areas—about one third was made up of hard white tissue, one third was pale white and not so hard, and the rest of the third was yellowish and comparatively soft. Other tissues removed at operation did not reveal any evident abnormality.

Histology :—The larger tumour on the left side showed small circular and ovoid groups of small polygonal cells separated by a scanty connective tissue stroma. The cell were almost uniformly polygonal in shape, their cytoplasm basophilic and their nuclei round and pale staining. There were a few blood vessels seen in the connective tissue stroma. Some sections showed areas of hæmorrhages and necrosis. 2. Sections from the smaller tumour from the right side showed a corpus luteum from one portion of the tumour. Part of the tumour consisted of dense fibrous tissue. The other portions showed small groups of medium sized polygonal cells separated by connective tissue. These cells like those of the tumour of the left ovary had basophilic cytoplasm and round and small nuclei. Some groups of cells showed vacuolation which may be an artefact. Histologically this tumour was a granulosa cell tumour.

The patient was under observation in the hospital for nearly a month. The X-ray showing disappearance of the fluid in the peritoneum and pleura was taken three weeks after operation. This meant immediate clinical cure. The pathological report does not suggest malignancy, though the sequence of events that followed would lead one to think of a malignant tumour. The following facts in the follow up will sufficiently make it clear that inclusion of this case under Meigs's syndrome on the mere evidence of happenings immediately after operation may not be justified.

The patient reported one month after discharge from hospital for a recurrence of ascites and was advised treatment by radiation. Whether she had it or not is not known. An attempt to trace her revealed from her husband the fact that she died nearly six months after she was operated on. There was no autopsy.

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PENICILLIN AND SULPHATHIAZOLE IN TYPHOID FEVER IN CHILDREN

G. Coelho *

INTRODUCTION

Bigger (1946)[2] reported that a combination of penicillin and sulphathiazole had a pronounced bactericidal effect on Bact. typhosum in broth and he suggested treatment of typhoid patients with sulphathiazole in full doses and penicillin in a dosage to maintain a concentration of 2 units per c.cm. in the serum. Evans[3] reported that the rate of growth of Bact. typhosum was retarded by penicillin, and that in mice who were inoculated intraperitoneally with the organisms the recovery rate was greater with those treated with penicillin. McSweeney[5] treated five typhoid patients with 200,000 units of penicillin two hourly and one G of sulphathiazole every three hours for four days, the course being repeated again after 2 days. He found "speedy disappearance of toxæmia, subsidence of pyrexia, and disappearance of organisms from the blood, fœces and urine at the end of the second course in three of the four cases." Parsons[6] collected the experiences of the physicians and nurses who treated and nursed patients in various epidemics in the military hospitals in the Middle East during World War II. "The conclusion drawn both by doctors and nursing sisters in the Middle East Fighting Forces was that treatment with penicillin and sulphonamides would have to produce much more dramatic results in the way of a rapid cure of the illness if the disturbance to patients of repeated injections was to be counterbalanced." Bevan *et al*[1]. treated adult patients in an outbreak of typhoid in Aberystwyth in 1946 and reported that their experience of the combined penicillin sulphathiazole treatment was "disappointing." They considered it necessary to warn against the indiscriminate use of this therapy. McSweeney[5] ascribed the failure of Parsons and other workers to what seemed to him insufficient daily and total dosage. Patel *et al*[7]. treated 9 culture positive typhoid patients with 2 G of sulphathiazole initially and 1.5 G four hourly for five days and 200,000 units penicillin intramuscularly every two hours until a total dosage of 10 to 12 million units were administered. They found the treatment beneficial, though the effect was not as striking as that obtained by McSweeney.

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Bevan *et al.* selected adult cases, but out of a group of 25 patients at Tanybwlch Fever Hospital 6 were children. Out of Patel's cases 5 were below 15 years, the youngest being 8 years old. Laha[4] reported on 7 children suffering from typhoid fever out of whom five were treated with penicillin and sulphathiazole. He found his results "very encouraging." The reports on typhoid fever in children treated with penicillin and sulphathiazole are few. Hence the following report is presented.

MATERIAL

Of the children admitted into the Byramjee Jejeebhoy Hospital for treatment of typhoid fever, between September 1947 and January 1949, 24 were treated with penicillin and sulphathiazole. The diagnosis in all patients was based on a positive Widal reaction ; in seven of these patients the clot culture was positive.

The selection of the cases was made on two grounds, (1) the seriousness of the condition, taking into consideration the degree of toxæmia and range of temperature and (2) the ability of the patients to purchase penicillin, though in deserving cases the hospital authorities supplied the drug from the Poor Fund.

The dose of penicillin varied from 30,000 to 50,000 units intramuscularly, every three hours, and of sulphathiazole from 0.5 gm. to 1 gm. four hourly orally. The total duration and the total dosage varied as shown in Table I. This dose is far below that recommended by McSweeney. Bevan *et al.* injected a 4½-year-old child with 2.4 mega units of penicillin in four days while the others received on an average 2.5 mega units per day. Patel *ct al.* did not decrease the dose for children. But Laha injected one child four years old with 15,000 units every three hours, and the other children aged 3½ to 9 years with 20,000 units three hourly. Compared to Laha's cases, the patients in this series received a larger dose.

The effects of the therapy on the toxæmia and temperature were studied. The toxæmia was judged by the general appearance, condition of the tongue, appetite, degree of awareness, blood pressure, delirium and signs of peripheral circulatory failure ; but above all it was the general impression. The effect on the temperature chart was easier to assess.

RESULTS

Of 13 patients who were toxic and looked very ill 7 showed an improvement during and after the treatment. In the rest the difference was not noticeable.

The temperature chart showed an improvement in 10 cases and none in the rest. The improvement in the fever has to be considered in relation

TABLE I

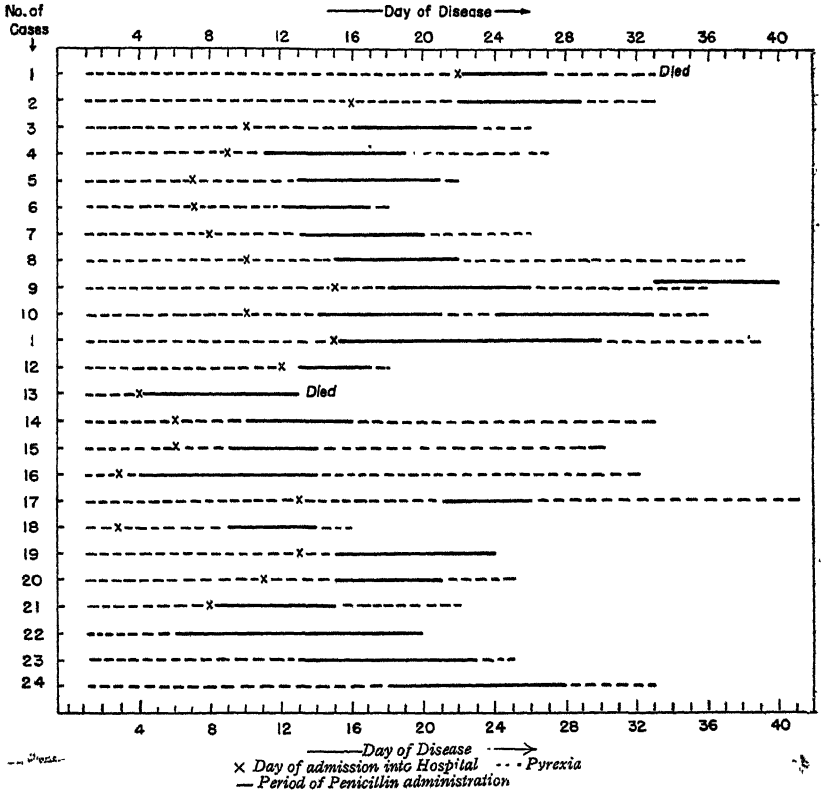
No.	Age.	Sex.	Day of disease.	On Admission		Widal.	Clot culture.	Days of disease of penicillin and sulphathiazole administration.	Total Dosage of Pencillin. (Mega units).	Total dosage of sulphathiazole in grams.	After treatment'		Temperature normal on	Remarks.
				Condition.	Temperature.						Toxæmia.	Temperature.		
1	12	M	22	Ill	101	O 1/500 H 1/500	—	22—27	2.1	30G				Improved slightly, died five days later.
2	11	M	16	Ill	103	O 1/250 H 1/125	—	22—29	1.68	36G	Imp.	Imp.		Improved.
3	9	M	10	Ill	101	O 1/1000 H 1/1000	—	16—23	2.2	42G	Imp.	Imp.	26	Improved.
4	7	F	9	Ill	101	O 1/750 H 1/750	—	11—19	3.3	60G	nil	nil.	27	
5	6	M	7	Good	102	O 1/500 H 1/250	—	13—21	2.6	21G	+	sl.	22	Improved.
6	5	F	7	Ill	101	O 1/250	—	12—17	2.3	15G	nil.	nil.	18	Sudden drop on the 17th day.
7	10	M	8	Ill	102	O 1/250 H 1/250	+	13—20	3.0	66G (11d)	+	+	26	Gradual up set.
8	10	M	10	Ill	105	O /250 H 1/50	+	15—22	2.75	18G	nil.	nil.	38	No Progress.
9	11	F	15	Ill	104	O 1/1000	—	18—26	3.2	72G (12d)	Imp.	nil.	36	No effect.
10	10	M	10	Ill	104	O 1/250 H 1/250	—	14—21	3.3	54G	Imp.	+	35	Improved.
11	10	F	15	Ill	104.5	O 1/1000 H 1/500	—	15—30	5.6	67.5G (15d)	+	+	39	Nil.
12	6	M	12	Sat	100	Para. A/1/100	—	13—18	2.0	15G (5d)	Imp.	Imp.	17	Good.

TABLE I—(*Contd.*)

No.	Age.	Sex.	Day of disease.	On Anmission.		Widal.	Clot culture.	Days of disease of penicillin and sulphathiazole administration.	Total Dosage of Penicillin. (Mega units).	Total dosage of sulphathiazole in grams.	After treatment.		Temperature normal on.	Remarks.
				Condition.	Temperature.						Toxæmia.	Temperature,		
13	1½	M	4	Ill	101	O 1/250 Para. A 1°250	+ B.Typ	4—13	3.6	4.5G (3d)	nil.	nil.		Died.
14	11	F	10	Ill	101	O 1/250 H 1/125	—	10—17	2.8	21G (7d)	nil.	nil.		Operated for suspected perforation—tabes mesenterica.
15	5	F	6	Fair	102	O 1/250 H 1/250	—	9—14	2.15		Imp.	nil.	30	No effect on temp.
16	8	F.	3	Fair	102	O 1/250 H 1/1000	+	4—14	3.0	60G	Imp.	nil.	32	No response. Responded to Paludrine. M. P. found.
17	9	F	13	Ill	102	O 1/250 H 1/150	—	21—26	1.6	32G	Imp.	Bet.	47	Poor response.
18	6	F	Rel. 3	Fair	101	O 1/1000 H 1/1000	+	9.14	1.9	2.5G	Imp.	nil.	10	Temperature not affected till 14th day.
19	5	M	13	Fair	102	O 1/150	—	15—24	1.89	27G	Imp.	Bet.	24	Improved
20	10	F	11	Ill	103	O 1/750 H 1/750	—	15—21	2.6	36G	—	—	25	Very little effect.
21	5	F	8	Good	103	O 1/250	+	8—15	2.1	18G	nil.	nil.	22	No effect.
22	3	F	6	Toxic	103	O 1/750	—	7—22	6.4	36G	Imp.	Imp.	21	Good effect.
23	7	M	8	Toxic	102	O 1/250	—	13—23	4.0	36G	Imp.	Imp.	25	Good effect.
24	10	M	10	Toxic	103	O 1/1000	+	18—28	4.0	40G	Imp.	Bet.	33	Satisfactory.

to the total duration of the fever. Chart I shows the day when the fever touched normal and interval between the cessation of the penicillin and the day the temperature touched normal.

TYPHOID FEVER WITH PENICILLIN



Observations on these few cases show that penicillin and sulphathiazole even in the dosage employed in this report are useful in cases of toxæmia. This is in accord with the findings of other clinicians. Their effect on the temperature is beneficial so far as the range of fever is concerned, but this therapy is ineffectual in reducing the period of the pyrexia.

In this series there was only one patient who suffered a relapse. The youngest child in the series, 1½ years old, whose clot culture was positive did not survive even though the treatment was instituted early and 50,000 units of penicillin were injected three hourly and sulphathiazole 1 G given every four hours. The latter had to be discontinued early because of vomiting.

Two patients received the treatment from a very early period of the disease—fourth day. Yet the effect on the course of the disease was not striking. One died on the 13th day. The second patient, whose clot culture was positive had the treatment till the 14th day, but the temperature did not touch normal till the 30th day. Here malarial parasites were found in the blood later and the fever yielded to Paludrine. In five patients the treatment was instituted between the 8th and 11th day of the illness; in only one the temperature touched normal on the 16th day while in the remaining four it did so on the 27th, 33rd, 30th and 22nd day. In this series administration of this therapy in the early days had not shortened the period of the illness.

Two patients had two courses each of penicillin and sulphathiazole at intervals of seven and five days, as the first course had no effect and the patients were still ill. The second course had a beneficial effect in the first patient, the temperature touched normal during the administration, and in the second, three days later. This was the 36th day—end of the 5th week and the tendency of enteric fever to touch normal at periods of weeks is well recognised.

Five patients received penicillin for ten days and over continuously. The effect on the temperature was striking.

CONCLUSIONS

In drawing any conclusions one has to remember that the dosage of penicillin is smaller than that recommended by McSweeney and so is also the number of patients treated. Even then penicillin together with sulphathiazole has a beneficial effect on the toxæmia in typhoid fever and subdues the range of temperature. There is no evidence that in the dosage employed in this series the period of the illness is curtailed, irrespective of the stage of illness at which the therapy is started.

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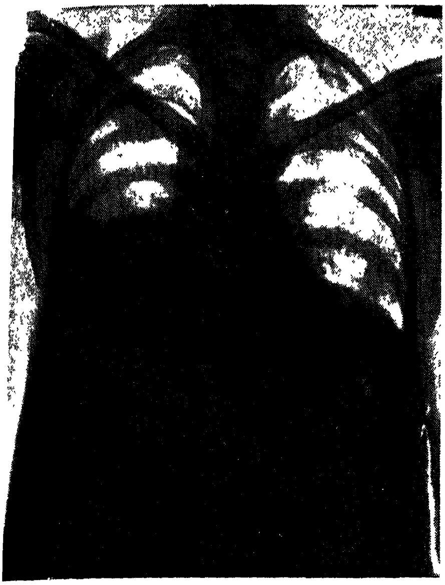

Fig. 1. X-Ray photograph to show effects of ascites and the level of the fluid in the pleura before operation.

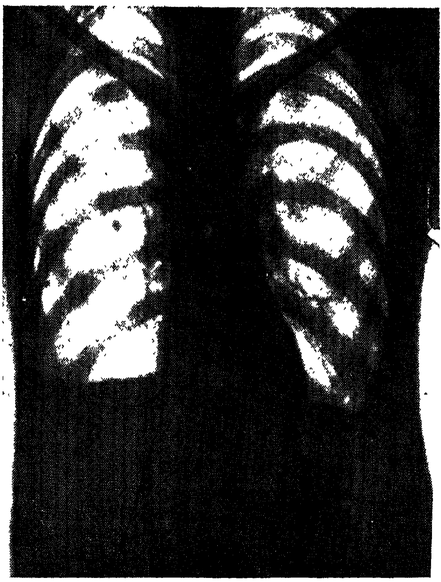

Fig. 2. X-Ray to show the result after operation.

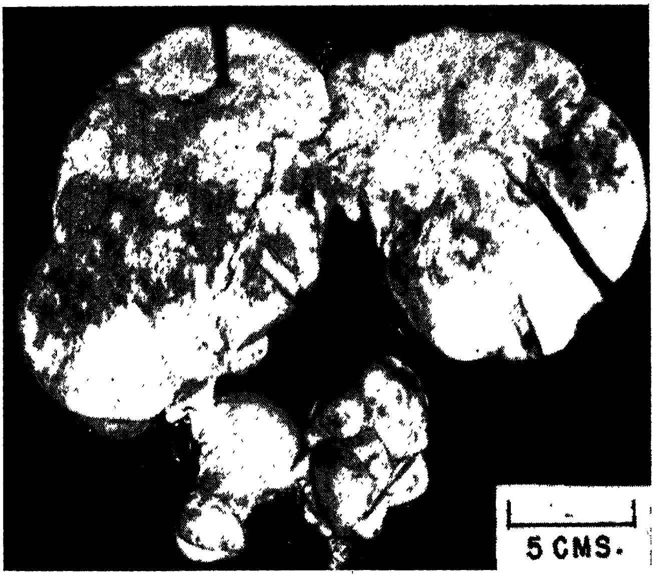

Fig. 3. The uterus with the ovarian tumours. The larger tumour has been cut and the halves separated.

PROGRESS IN THERAPEUTICS, 1948

V. Iswariah *

A steady advance in therapeutic management is in evidence during the past few years; one may say that the spotlight has been focussed once again on chemotherapy. Drug therapy at the commencement of this century was gently knocking the portals of medicine for entry. Today she has not only entered the hall of fame in medicine but threatens to close the door for other entrants. Who will fail to observe when opening the pages of any medical periodical these days, the announcement of some new therapeutic agent or an old drug for yet another disease or an improved substitute? Does the old banter "Medicine sometimes cures, often relieves, always consoles" hold ground today? The aim of therapeutics is no longer 'will do no harm' but 'will do some good.'

I. TROPICAL DISEASES AND CHEMOTHERAPY

Tropical diseases have had the special attention of chemotherapy; pencillin, sulpha drugs and paludrine far from making therapeutics rest on its oars have rather given the incentive and fillip of the right sort and in diverse directions. Progress has not only been made in the treatment of tropical diseases like cholera, plague, leprosy, filariasis etc. but chemotherapy is fascinatingly extending her benevolent arms to embrace malignant diseases. The new British Pharmacopoeia (official from September 1948) is a striking testimony to the advance of therapeutics.

One feels that chemotherapy of tropical diseases should claim our early attention.

CHOLERA

Textbooks on therapeutics had often commenced the subject of treatment of cholera with the words "....there is no specific treatment of cholera but...." The 'non specific' treatment then consisted mostly of combating dehydration. Sometimes attempts were made to treat the condition by medicaments like permanganate of potassium, essential oils (Tomb's), kaolin etc. But the attempt could not be designated 'Chemo-

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therapy'. Sulphaguanidine and allied compounds have been tried, but several reports failed to support their utility. At this stage comes a new compound (not yet 'christened') going by the designation "6257," a condensation product of two molecules of sulphathiazole with three molecules of formaldehyde, claiming to effect 'substantial relief' in cholera. The starting point for this investigation was an accidental observation that 10% hexamine in saline killed cholera vibrio in half an hour. Linking hexamine with sulpha compounds gave more promising results. "6257" or $C_{12}H_{22}O_6N_6S_4$ seems to act in cholera not as an improved sulpha compound substitute but with a type of action all its own. The compound is relatively insoluble, slowly absorbed by gastric route and slow of excretion. Though parenteral administration does not cause appreciable irritation, there is tendency for depot formation and hence is indefinite as regards absorption. If vomiting is severe, rectal route is suggested. Bhatnagar and Devekar (1948)[1] have claimed after extensive trial in S. India, that 4-8 G doses of "6257" in acute cases of cholera revealed within 24 hours perceptible improvement. Vomiting and purging ceased, urinary output was increased and even symptoms of dehydration relieved. The scheme of dosage suggested is a gradual decreasing one of 6, 5, 4, 3, 2, 1, 1, G for about seven days. A higher initial dose may be necessary for severe attacks. If the medicament was not retained when administered orally in one big dose, it was suggested that smaller doses with sips of water at intervals of 5-10 minutes might be tried. Copious drinks of water with soda bicarb. at frequent intervals are recommended. On or about the fifth day of treatment, cholera vibrio were completely absent from the stools. The mortality rate according to them was reduced from 60% to 4%.

PLAGUE

Bacteriophage, vaccines and antisera not having come up to expectation in plague, sulpha drugs were tried. The results were indeed encouraging. Sulphathiazole 2-4 G followed by 1 G four hourly for 36-48 hours have been reported to give very satisfactory results. But cases that failed to respond to sulphathiazole, reacted most favourably to streptomycin. Doses of 0.125 G every three hours for 36 hours or more restored to life several cases of all the varieties of plague that were deemed moribund.

LEPROSY

The agelong use of hydnocarpus or chaulmoogra preparations in the treatment of leprosy did not mean that their specificity in leprostic infections was established, though Rogers believes that they do destroy the leprosy organism.

During the last few years the introduction of sulphones in the treatment of leprosy has revealed fresh prospects. In 1939 it was reported that promin or 4.4 diamino diphenyl sulphone inhibited growth in vitro of human and avian tubercle bacilli. This compound is relatively insoluble and thought too toxic for human use. Promanide, a more soluble derivative was tried with no appreciable improvement. Since the two acid fast organisms of tuberculosis and leprosy resemble in many bacteriological aspects, the sulphones were tried in leprosy. When given in 3-5 G doses daily intravenously, results were very encouraging. In 1944 came diasone or disodium formaldehyde sulphoxylate diamino diphenyl sulphone and was tried in lepromatous leprosy. It was less toxic by mouth than promanide and could be given in 1 G doses daily for several months. Clinically, lepromatous condition was visibly arrested and the drug had a boom in the lay press as a 'Cure' for leprosy. Promin itself is used by many with satisfactory results. The drug could be administered even during the flare up period, when it tended to sedate many of the acute symptoms of the flare up. Other sulphones now under investigation are promizole or 4.2 diamino phenyl thiazolyl sulphone and sulphetron or 4.4 bis phenyl n-propyl amino diphenyl sulphone tetra sodium sulphonate.

In all these sulphone derivatives it looks as though the parent sulphone radical is the main active agent, like the sulphanilamide radical in some of the amino substituted sulpha derivatives like prontosil, proseptasine, rubiazol, etc.

But toxic manifestations are not infrequent with the sulphones. They are, hæmolytic anæmia, gastro-intestinal disturbances, febrile reactions and rarely agranulocytosis. Experience suggests that with cautious dosage some of the toxic manifestations could be avoided. A watch on the blood condition is necessary when using the sulphones. Once the system gets used, treatment for a prolonged period, even a year could be resorted to with good chance of arrest of leprosy. The response in lepromatous type warrants its trial on a large scale provided cost and availability are not insuperable factors.

As in tuberculosis, the antibiotics like streptomycin promise to be of value in leprosy. It is a happy augury that synergism exists between the sulphones and streptomycin and this may carry us a little further towards the cherished goal of eradicating leprosy. Diasone promises to be of value in the treatment of actinomycosis.

II. SULPHA COMBINATIONS

The use of sulpha combinations since their introduction has revealed interesting facts. Each constituent of the combination, usually Sulpha-thiazole, diazine and merazine (Sulphatriad) retains its individual solubility in urine, thereby reducing the chances of precipitation and toxicity. Observations were further made as regards sensitisation to sulpha compounds when administered singly or in combinations. Lehr (1948)[2] studied the factors governing sensitisation with sulpha drugs, like varying dosage, duration of treatment, intrinsic nature of the compound used etc. What share has each one of these to produce sensitisation ? His criteria for sensitisation were drug fever and rash. The smaller the daily dose, the less likely is sensitisation, irrespective of duration of treatment. On the other hand six grams daily dosage or more showed sensitisation more often. Two grams daily of any sulpha compound for a period of one month did not cause sensitisation. A blood concentration of 5 mg. per 100 c.c. should never be exceeded according to him.

Again, sensitisation is specific for a particular drug whether one, two or more are administered in combination. The chances of sensitisation will depend on the concentration each drug attains in the blood and tissue and not on the total sulpha concentration when more than one is given. In other words there is no 'cross sensitisation'. It is therefore to be expected that sulpha combinations are less likely to sensitise than when the same dose of a single compound is administered.

If these observation are confirmed, a strong case has been made for sulpha combination therapy. Possibly the same principle may be extended to several pharmacologically related compounds but with different molecular structure like the thiouracil derivative, barbiturates, etc.

DARVISUL

Darvisul or phenosulphazole or N2 thiazolyl phenol sulphonamide is a sulpha derivative and is reported to be effective against the virus of poliomyelitis. Mice and monkey tests were encouraging and reports of clinical success are eagerly awaited. The drug seems to act on the cell infected with the virus, changing its physiology and making it an unsatisfactory environment for the virus to grow.

The activity of the compound is inhibited by parahydroxy benzoic acid (not to be confused with para aminobenzoic acid). (This compound, with hetrazon for filariasis and folic acid for pernicious anæmia are of special interest as they are associated with the name of Dr. Y. Subba Rao of Lederle, a rare Biochemist, an Andhra and an Indian, who met with death prematurely in 1948.)

III. ANTIBIOTICS

RADIOACTIVE PENICILLIN

Penicillin is here made to incorporate a sulphur isotope S35 into its molecule. Observations made after administering ordinary penicillin, labelled penicillin and mixed ones to animals showed that 100 per cent. of the radioactive sulphur isotope was excreted in the urine, but the recovery of biologically active penicillin was much less. Orally administered tagged penicillin-acted in a manner similar to the untagged one. These data so far find no useful therapeutic application.

PROLONGING PENICILLIN ACTION

More work has been done in an attempt to prolong penicillin action after the use of para amino-hippuric acid, caronamide, diodrast, etc. Caronamide is said to interfere with tubular function and the appearance in some cases of a reducing substance in the urine of patients who had been administered caronamide, suggests the possibility of disorganised cellular metabolism. Caronamide is therefore to be used with caution. Penicillin absorption from depots is also delayed by a base containing gelatin, dextrose and a vaso—constrictor. Potassium penicillin in vegetable oil with adrenaline also exerts a prolonged action, while some claim similar results with relatively insoluble penicillin compounds. An equimolecular procaine penicillin compound is used as a suspension in cotton seed oil or oil of sesame without beeswax. (Beeswax often produced sterile abscess.) The procaine penicillin compound has low solubility in addition to the local anæsthetic action of procaine. A single large dose of penicillin in this form may maintain optimum penicillin level in blood for over 48 hours. Cases of pneumonia, gonorrhoea etc. have been successfully treated with one dose. This is so far deemed the method with the greatest degree of prolongation of penicillin blood level. (Duracillin is the commercial name for this compound.) For treating syphilis 3 lakhs daily, for about 2 weeks, of this penicillin procaine-oil compound seems to be satisfactory, other adjuncts not excluded.

It looks as though the original watery solution of penicillin will, ere long, be obsolete for ordinary therapeutic use.

Addition of a water repellent substance like aluminium monostearate to suspensions of procaine penicillin further prolongs the action.

PENICILLIN AND SUBACUTE BACTERIAL ENDOCARDITIS

Penicillin holds out hope in the treatment of subacute bacterial endocarditis. Upto 1943, the condition was deemed an incurable one, but with penicillin and decumerol one is in a position to transfer the analogy of Kala-Azar *vis a vis* antimony and say that 90 per cent. mortality or morbidity could be converted into 90 per cent. cure or recovery.

STREPTOMYCIN—SOME PHARMACOLOGICAL OBSERVATIONS

Streptomycin can be given orally and is not destroyed in the gut, but absorption is indefinite. It has been used with good results in infantile gastro-enteritis.

Excretion of streptomycin in animals reveals that nearly half is excreted in the urine. More than half of the amount so excreted in the urine retains the original potency. The overall recovery is therefore about a quarter of the total administered if the entire urine is collected. It is for the 'chemical economist' to offer suggestions for conserving this precious medicament which is in short supply today.

STREPTOMYCIN SENSITIVITY

A distressing side action of streptomycin has been noticed in persons handling this product. A dermatitis consisting of a papular erythematous rash, itching particularly round the eyes and elbows have been noticed. Skin tests for detecting sensitivity revealed that all patients who had dermatitis after handling streptomycin were positive to the test. Symptoms develop usually after a month, sometimes as late as six months after exposure. Those who are to handle this antibiotic frequently are advised to wear gloves. It will be unfortunate if an idiopathic sensitivity exists and that everyone prescribed streptomycin is to be subjected to a prior skin test. It is not possible at this stage to say if this sensitivity is due to an impurity or to the purified stuff itself.

(It may not be out of place here to mention that some observers of late have felt that the imperfectly purified penicillin of earlier days was more effective than the present highly refined products. The attempt to remove the alleged "toxins" in penicillin that gave side effects has also tended to rob it of therapeutic potency.)

TOXICITY

At a Streptomycin Conference sponsored by the National Research Council (1946)[3] it was observed that the old regimen in tuberculosis of 2 G streptomycin daily for 100 days or more showed in over 95 per cent of cases, subjective and objective symptoms of vestibular damage. Vertigo, tinnitus, deafness, blurring of vision, dermatitis and rarely kidney damage were noticed.

STEPTOMYCIN AND TUBERCULOSIS

The three types of tuberculosis said to respond to streptomycin therapy are the ulcerative laryngobronchial, the meningeal and the acute miliary. But the cure in all these is not absolute or 100 per cent. Hurry to streptomycin therapy when other time honoured ones are available is fraught with risks, as resistence to streptomycin is frequent. (Those interested in this subject are referred to the Medical Research Council investigation on streptomycin treatment of tuberculosis published in the Brit. Med. Journal Oct. 30,1948.)

Resistence of tuberculosis organism to streptomycin seems to be a real and distressing problem today. In long continued use of streptomycin in tuberculosis, it has been observed that resistance to this antibiotic is serious and significant though its genesis is obscure. Mayo clinic investigations (1947)[4] revealed that if there was 1 in 88,750 resistant tubercle bacilli before treatment with this antibiotic, after two weeks of treatment there was 1 in 13,000, after three weeks of treatment 1 in 800 and 1 in 350 after four or five weeks of treatment. It was also noticed that the drug resistant strains grew more slowly and developed smaller colonies, suggesting thereby that there is considerable interference with their vitality. Of course there were scanty initially resistant strains. The position is more or less similar to penicillin therapy of staphylococcal infections, the resistant staphylococci are said to have been trained to produce penicillinase which destroys the active antibiotic. Are massive initial doses in acute infections the remedy, or intermitent therapy for subacute conditions or combined therapy with different chemotherapeutic agents ?

Voureka (1948)[5] has made the fascinating suggestion that resistance could be changed into sensitivity by 'sensitisation' with other bacterial cultures or their filtrates. Does that mean that in a resistant case of tuberculosis, vaccine or toxin of some other organism administered to a patient as a substitute for streptomycin for a short period renders the resistent tubercle bacilli susceptible over again ? This interesting finding should open the flood gates for investigations in an attempt to circumvent this annoying habit of organisms to develop resistance.

STREPTOMYCIN IN SURGERY OF BONES AND SINUSES

Report again comes from Mayo clinic (1948)[6] that cases with tuberculosis of bones, joints, sinuses etc. responded to 3-4 months streptomycin therapy. One to two grams of streptomycin were administered daily for over a month. Considering the difficulty encountered in treating these conditions by other methods, this line of treatment was deemed very satisfactory.

ANTIBIOTICS AND VENEREAL DISEASES

The two recent chemotherapeutic agents sulpha drugs and antibiotics seem to have successfully vanquished all the five venereal diseases. Penicillin claims to have conquered gonorrhœa completely and syphilis partially, the sulpha drugs chancroid and lymphogranuloma in addition to gonorrhoea. Data are now available for streptomycin attacking granuloma venereum and chloromycetin and aureomycin (to be referred to later) lymphogranuloma. Four grams of streptomycin daily for four or five days hastened the healing process in granuloma venereum and within the end of a fortnight the healing process was almost completed. No recurrence was noticed for a period of about three months after the cessation of treatment or after completion of the healing process. Longer observation should establish the claim that streptomycin is more effective than antimony ; some light may also come on the etiology of granuloma venereum.

Another observation of interest is that a single dose of 0.2-0.5 G of streptomycin has been found to be effective in gonorrhœa without masking any subjacent treponema infection.

With aureomycin not only does the lymphadenitis of lymphogranuloma responds but even the anorectal stricture gives evidence of improvement.

These are very fruitful observations in the realm of venereology : a surgeon rightly observed that ere long elaborate venereal clinics will be rendered futile and venereal specialists unnecessary.

STREPTOMYCIN IN OTHER CONDITIONS

In the treatment of long-standing urinary infections, when multiple organisms are found, streptomycin has been found to be superior to sulphadiazine and sulphathiazole. The tendency to crystalluria in acid urine is obviated by the use of streptomycin ; resistent strains are also less frequent. Streptomycin has also been found to be 80 times more effective if the urine is rendered alkaline to pH 8. (A new synthetic substance mendalamine or methanamine mandelate promises to be as effective as streptomycin in chronic urinary infections.)

In Brucellosis, 2 G sulphadiazine and 1 G streptomycin eight hourly intramuseularly for ten to fourteen days gave good results in manyinstances. Penicillin is ineffective and streptomycin by itself was unsatisfactory. In experimental animals, 5 c.c. of 5 per cent. sodium paraamino benzoate every four hours for about 2-3 weeks completely eradicated infections of *brucella melitensis, br' siussins and br. abortus* and this finding is being translated to human needs. This is an interesting finding as paraamino benzoic acid which is an essential metabolite for some organisms here seems to act as a poison.

NEWER ANTIBIOTICS

BACITRACIN

This new antibiotic is obtained from cultures of an aerobic organism which is Gram positive and spore forming. It is active against many groups of staphylococci and even the strains resistant to penicillin and sulpha drugs. When locally used it is non-irritating, not inactivated by pus, blood, plasma and what is more interesting is unaffected by organisms that produce penicillinase. Its value is mainly in infections with a mixture of pathogenic organisms.

CHLOROMYCETIN

Atleast five antibiotics are produced by various species of streptomyces isolated from soil. Streptomycin is the outstanding member, while streptothricin isolated earlier is practically discarded. The others are chlormycetin, aureomycin and grisein. Chlormycetin had a boom lately as a 'Specific' for typhus. Four to eight grams of chlormycetin in 24 hours divided for three or four hourly administration, followed by reduced dosage on three or four subsequent days greatly reduced mortality in typhus according to the Malayan scrub typhus investigators. Oral administration is a great advantage with this antibiotic. It is active not only against rickettsiases, but also against virus of psittacosis-lymphogranuloma group. The crystalline form in solution is more stable than penicillin and in a greater acid range than streptomycin. Chlormycetin can be heated to 100 deg. C for five hours but parenteral route causes irritation. Chlormycetin also holds out hope for typhoid. Aureomycetin, another antibiotic closely allied to chlormycetin has similar properties chemically and clinically.

AUREOMYCIN

This is derived from streptomyces aureofaciens and is active against numerous Gram positive and Gram negative organisms like strepto Lancefield, strepto fæcalis, bacteria pneumonia, strepto pneumonia, hæmophilis influenza etc. It is more effective against the virus of Rocky Mountain Spotted Fever, lymphogranuloma, brucellosis in 20-30 mg doses intramuscularly daily. Aureomycin also promises to be a valuable addition to the armamentarium of the ophthalmic surgeon in many kerato-conjunctival conditions like infective conjunctivitis, Mooren's ulcer, dendritic keratitis, epidemic kerato conjunctivitis (S. P. K. ?) etc.

GRISEIN

From certain strains of streptomyces griseus seems to synergise streptomycin and tends to prevent streptomycin resistance. It is of some value in infections with coliform organisms.

POYMYXIN AND AEROSPORIN

These two closely related antibiotics are active against Gram negative organisms unaffected by other antibiotics like the salmonella group, shigella, etc. Bacillus polymyxin is a soil organism, from the fermentation liquid of which polymyxin is obtained. Aerosporin is from an aerobic bacillus called 'Bacillus aerosporinx Green.' As available today, they tend to be toxic since their purification process is not completed. Chemically the two substances appear to be polypeptides, and on acid hydrolysis yield amino acids like leucine, threonine, sirine etc. Neither of these penetrates the blood brain barrier. Aerosporin has also been found to be effective in pertussis when administered parenterally in 5 mg. doses every four hours.

TYROTHRICINE TOXICITY

The older antibiotic tyrothricin was used topically in several conditions. When used for irrigating nasal sinuses, alarming and disastrous effects were noticed in a good few cases by inducing a chemical meningitis. Experiments conducted subsequently on dogs confirmed the view that tyrothricin acted as a chemical irritant particularly in the region of the cisterna magna leading on to a severe form of meningitis. This is a note of warning to otorhinologists.

The wave of antibiotics had pushed many a member to the fore, but gramicidin, tyrothricin, streptothrycin, patulin, actinomycin etc. have not asserted their value; they are receding.

IV. ANTIMALARIALS

PALUDRINE

The boom and the drumbeat with which paludrine was hailed is gradually yielding place to more sober appraisal. Neither paludrine nor chloroquine has been able to prevent the establishment of vivax infections in the human even by daily use, much less after bi-weekly or weekly administration. After a month of cessation of treatment with paludrine, relapse has been noticed—relapse definitely and not re-infection. Certain types of falciparum malaria of Africa demand a heavier dosage than what was originally recommended for suppressing acute attacks. After the acute attack, 100mg, daily is recommended by some as suppressive dose while for a radical cure 300mg t. d. s, for ten days is suggested, In a previous article on this subject (*vide* Ind. Jr. Med. Sc., 635, 1948 635) the writer had observed "One hears little these days of pamaquine nor of the so called 'standard treatment' of malaria". A challenge to this has come from Monk (1948) [7] by his observations on quinine and pamaquine. Monk is of the view that quinine with pamaquine had an effect on the suspected exo-erythrocytic form or pre-erythrocytic form. Paludrine given concurrently with quinine had also equally good effect. Hence pamaquine is not merely a 'gametocyde'. The toxicity of pamaquine had always been emphasised but it is to be considered if its alleged toxicity is really formidable or menacing. Pentaquine was synthesised with the hope that it would be much less toxic than pamaquine, but in reality it is atleast 50 per cent. as toxic as pamaquine. In Monk's study a month's intermittent course of quinine and pamaquine gave better results in vivax infections than daily paludrine administration; the aim being complete eradication of the infection. In 60 mg. doses pentaquine appreciably reduced relapses in vivax malaria while combination with quinine did better. In severe vivax infections while quinine by itself had negligible effect, pamaquine moderate effect, pentaquine slightly better effect, concurrent quinine and pentaquine had given the best results. Whether quinine potentiates pentaquine or each contributes independently for the ultimate suppression of relapses it is difficult to say. Pentaquine in 60mg. doses with 2 G of quinine daily in four divided doses for 10-14 days, reduced relapse rate considerably. The toxic manifestations of pentaquine, though definitely less than of pamaquine consisted of anoxia, prostration, syncope and occasionally hæmolytic anæmia. After daily dose of 90mg. of pentaquine for about a fortnight, toxic manifestations persisted for about a week. It is interesting to note that in Monk's series, hæmolytic anæmia was noticed only in coloured patients. Hence 60mg. is about the maximum dose permitted in the acute phase and half of it as suppressive measure. Treatment had to be given only to hospitalised patients as 60mg. dose for a week often caused toxic effects.

CHLOROQUINE AS AMOEBICIDE

An interesting observation regarding the action of chloroquine is that in vitro it had an amœbicidal activity greater than carbarsone and perhaps a little less than emetine. In human amœbic colitis, 0.3 G of chloroquine B. D. for 2 days and 0.3 G daily for about 10-15 days subsequently, freed the stools of amœba for about a year. In amœbic colitis, symptoms and signs disappeared spectacularly within four or five days of the start of the above treatment. As chloroquine is completely absorbed from the gut, the effect on amœba in the colon must be due to plasma or tissue concentration.

ANTIMALARIAL DRUGS AND THEIR PHARMACOLOGICAL ACTIONS

Very interesting pharmacological observations have been made on the antimalarial drugs. Mepacrine when injected intravenously diminished the inhibitory action of vagus on the heart. Quinine showed a similar action. Since quinine and quinidine are able to arrest auricular fibrillation, it suggested itself that mepacrine would also be effective. In a series of eight patients Gentlen and Yohalen (1948)[8] observed that normal rhythm was restored in auricular fibrillation by using mepacrine. They had given mepacrine by the intramuscular route with 10 c.c. of 1 per cent. procaine. Procaine has also the property of lengthening refractory period in auricular fibrillation.

Paludrine was also found to diminish the action of vagus on the heart. Quinine and mepacrine when adiministered intravenously reduced the secretion of gastric juice which is produced by stimulation of vagus. Mepacrine counteracts the effects of insulin in augmenting gastric secretion. Paludrine was noticed to diminish the effects of histamine on gastric secretion. This finding promises to be of use in the treatment of peptic ulcer.

In all these studies, fairly large doses of the respective antimalarials were used. These findings are just in the preliminary stages offering considerable interest; they have not been put to therapeutics so far. The surprise of these findings is that the three antimalarials *i.e.*, quinine, mepacrine and paludrine are not chemically similar. Pamaquine is perhaps more closely allied to quinine though the side chain in pamaquine and mepacrine are identical.

V. HETRAZON AND FILARIASIS

Considerable experimental work including clinical trials have been carried out since the announcement that hetrazon is a new anthelmintic against filariasis. Experimental work has been considerably facilitated by the finding of a naturally occurring filarial infestation (litomosides carini) in cotton rat, an animal that readily lends itself to experimental work as against the dog experimentally infected with heart worm (dicrofilaria immitis). Experiments with cotton rats infested with filaria show beyond doubt that hetrazon in 24-36 hours clears the peripheral blood of all microfilaria with later evidence of destruction of the mother worm. In dogs, after two weeks of treatment, microfilaria disappear from the peripheral blood. The effect of the parent worm seems to depend on the dose, frequency and the number of days interval from cessation of treatment to autopsy. Though originally a scheme of 1-2mg. per kilo B. D. or T. D. S. for two, three or four weeks was suggested, better results were obtained with 10 mg. per kilo twice a day for two or three weeks. In some cases death of a large number of worms and embolus formation in the pulmonary artery tended to risk the life of the experimental animal. The blood remained negative for about three months of cessation of treatment. Trial on human subjects with microfilaria in the peripheral blood has so far elicited satisfactory response in that there is progressive reduction of peripheral microfilaria in the course of the treatment. Extensive trials are now being carried out in the King George Hospital, Vizag., and in the Madras General Hospital. In the specified therapeutic dose, the drug has so far been singularly free from toxic side reactions. Occasionally 10mg. per kilo dose showed enlargement of lymph nodes, lymphadenitis, pyrexia etc. but none of them of a serious nature.

A number of cyanine dyes were also found to inhibit the oxidative mechanism of adult filaria. In 0.1 mg. per kilo dose every 8 hours, for about 18 doses, the adult worm in cotton rat was destroyed. The drug is administered intraperitoneally. Human experiments have been inconclusive.

VI. CHEMOTHERAPY AND MALIGNANCY.

Chance, enthusiasm over the success of chemotherapy in other realms, limitations of surgery, costliness and practical difficulties of radiotherapy are making malignant diseases look in other directions for succour. To be fair it has to be said that it is the understanding of mechanism of radiotherapy that is opening the gates of chemotherapy to malignant diseases.

The metabolism of malignant cells is not yet sufficiently clear to permit prognostication as to the rational point of attack of chemicals. As far as it is understood, the mode of action of radiotherapy seems to be by altering the metabolism of an abnormal cell by inducing structural changes in the chromosomes leading on to fission, reunion, interchange or destruction. Radiotherapy at all times has been a double-edged weapon with stimulant and depressent actions, creative or destructive in its potentialities.

Biochemically, radiation, depending on dosage, interferes with the synthesis of thymonucleic acid which in turn initiates a series of far-reaching disturbances of an anabolic or katabolic nature. Cannot chemotherapeutic agents like radioactivity initiate similar changes in the metabolism of cells ? Prior to the earliest record of real chemotherapy in cancer, it was observed in 1867, that an attack of erysepelas caused regression of cancer in some patients. Coley then tried several filtrates of various bacteria in cancer patients and noticed multiple hœmorrhages in the tumour, with a tendency to regression by necrosis of scattered bits of tissue. A highly active hæmorrhage-producing agent was obtained from *B. prodigiosus.* Chemically the material used was a polysaccharide and its effect was anoxia due to diminished blood supply, leading to necrosis and possibly incidental hæmorrhages. Subsequently it was revealed that the polysaccharide was a general systemic poison and that the tumour which developed after some time was refractory to further treatment. An interesting side observation was that while in experimental animals there was a fall in body temperature with the polysaccharide, there was a rise in temperature in the human.

RADIOACTIVE ISOTOPES AND MALIGNANCY

After radiotherapy in the treatment of malignant diseases the next step was the introduction of radioactive isotopes popularly known as tagged elements like radioactive phosphrous in polycythemia, radioactive iodine in thyroid conditions etc. This line of treatment is just another form of radiation therapy, differing from X-ray or radium therapy in that the chemical can be administered orally or parenterally to get distributed in the body evenly or selectively in organs and from there exert 'irradiation'. Some tumours are said to take up more radioactive phosphorus than normal tissue. Lymphomatous tissue retained greater amount of some isotopes. Studies in the distribution of isotopes in leukæmia showed that organs with high infiltration of leukæmic cells like spleen, liver, kidney, bone marrow etc. had greater deposits of isotopes. Thus localisation combined with differential absorption of the rapidly multiplying leukæmic cells provided the necessary basis for this form of therapy.

So far, X-ray therapy and P^{32} run parallel in their utility in some malignant conditions, with the added advantage for phosphorus that it does not produce radiation sickness. On the other hand where massive radiation for localised effects are desired, X-ray is to be preferred. A pharmacological fact of interest is that iodine is largelly localised in thyroid, strontium in bone, phosphorus in bone marrow and rapidly growing leukæmic tissues while sodium is distributed evenly in the extracellular compartment of the body.

RADIOMIMETIC SUBSTANCES AND MALIGNANCY

The next stage in the treatment of cancer was the use of 'radiomimetic' substances whose action could be conceived as truly chemotherapeutic in nature. The abnormal nature of a malignant cell, its susceptibility to certain chemicals, affinity of certain chemicals for certain abnormal cells, freedom of normal cells from the effect of the chemical etc. are factors to reckon in this form of treatment.

Nitrogen mustard in Hodgkin's disease and urethane in leukæmias seem to subserve the above requirements. There is no radioactivity about nitrogen mustard nor urethane, but their effect on abnormal cells resembles that of irradiation. These observations take one to the next step.

HORMONES AND THEIR SUBSTITUTES IN MALIGNANCY

Oestrones stilboesterol, testesterone etc. were noticed to inhibit cell multiplication in malignancy by interfering with the metabolism of nuclei of cells. Experimentally it was known earlier that pure and synthetic æstrogens were capable of inducing mammary cancer in breeding female rats, sometimes in virgin rats and occasionally even in male rats and mice. The action of oestrogens seem to be to accelerate the development of mammary glands as a prelude to development of cancer. (Genetic factors and hormonal stimuli play a large part in rat cancer.) Reversing the process has led us to the use of oestrogens and stilbœsterol in prostatic cancer and testesterone in breast cancer. Corticosterone and its substitutes are also reported to have an inhibitory effect on experimental lymphosarcoma in animals. Recently the medical research council had published the effect of an extract of male urine designated H11 in the treatment of malignant diseases. (*Vide* B. M. J. Editorial p. 716 Oct. 16. 1948) That growth controlling agents are present in tissue extracts and urine has been known to physiologists. Experimenters have attempted control of cancer by using extracts of placenta, gonads, thymus, muscles, connective tissue etc. Some of these produced ostensible benefits such as relief of pain, improvement in the sense of well-being and occasionally even regression in the size of the neoplasm. With H11 or the extract from male urine, there was no evidence of inhibition of malignant diseases. (This finding seems to have provoked to anger some who were optimistic about the utility of H11 and received the findings of the Medical Research Council with disfavour.)

VITAMINS AND MALIGNANCY

The next stage in the treatment of malignancy is with vitamin products. Experimentally, in transplanted sarcomas in mice, the growth of tumour was arrested in some and regressed in others with folic acid concentrates. When human beings with cancer were administered folic acid derivatives, a marked subjective feeling of wellbeing was noticed with reduction of pain thereby leading to withdrawal of morphine and other analgesics. No appreciable reduction in the size of tumour was noticed. Biochemically there was a marked reduction of the abnormally high alkaline and acid phosphate value.

Teropterin and diopterin are two derivatives of folic acid, teropterin being pteroyl tri-glutamic acid while diopterin is pteroyl di-glutamic acid. Pharmacologically, teroptern was more effective in relieving pain and conferring a sense of comfort. It is at present a subject of study if the two compounds have a mere non-specific analgesic action or if the relief of pain is due to regression of tumour growth.

A puzzling further finding was that folic acid derivatives in some cases actually accelerated the condition of malignancy as in leukæmias. This observation induced some investigators to try 4. amino pteroyl glutamic acid which is an antagonist of folic acid. Remissions were noticed in over 60 per cent. of cases. But natural remissions are possible in acute leukæmias and hence the findings have to be guardedly assessed. The above folic acid antagonist or aminopterin was replaced by 'A. Methopterin' which was less toxic and more active in smaller doses. Similarly a pyridoxin antagonist was found to cause regression of lymphosarcomas. These findings are of twofold interest in one, that vitamins and hormones are closely linked in action and two, that chemotherapy of malignancy is not a mere idle dream.

OTHER CHEMICALS AND MALIGNANCY

Since 1943 several chemical substances were found to produce gene-mutations and rearrangement of chromosomes similar to X-rays and gama-rays. In some instances when the cells had developed radio resistance, chemicals were capable of effecting chromosome rearrangement or interference with the metabolism of nuclei of the proliferating cells. More interesting was the observation that in many radioresistant cases, chemotherapy had made the cells radiosensitive subsequently. One such chemical is Colchicine which was found to arrest mitosis in tissue cultures and tumour cells, but was too toxic for routine use as doses only just below m.l.d were able to arrest growth and even this dose was too toxic to the C.N.S. Like bacterial metabolites, it caused hæmorrhage and necrosis of tissue. Colchicine like X-ray was active against rapidly growing tumours. Following colchicine administration, there was a sharp drop in the ascorbic acid content of tumour cells, in glycolysis and respiration. Other compounds that resemble colchicine in these actions are acriflavine, sodium cacodylate, auramine (a dye used as antiseptic for skin) etc. One should not omit to mention the old use of benzene and liquor arsenicalis in malignancy. In some kinds of myeloid leukæmias they were effective, while benzene was also effective in lymphoid leukæmia and chloroleukæmia. In no sense was cure effected, but it is surmised that survival period was prolonged.

Another series of compounds found to possess similar lytic action on malignant cells were the diamidines. Stilbamidine (used in kala azar) and pentamidine (used as surface antiseptic) showed favourable effects in some cases of myelamatosis. There was significant relief to pain and an alteration in the cytoplasm of myeloma cells, a precipitate of ribonucleic acid with the diamidine being formed. Presumably the nucleoprotein of myeloma cells is different from that of other cells in the body and stilbamidine has a specific affinity for these.

URETHANE AND NITROGEN MUSTARD

The present position could be summarised in the words of Mitchell (1948)[9] "... thus far apparent cure of leukæmia by urethane has not been recorded. Though the use of urethane is not without danger, it may be of use as an adjunct to X-ray therapy in myelogenous leukæmias. The remission under nitrogen mustard chemotherapy of leukæmia, lymphosarcoma and other 'cancers' present openings for further research".

From a review of clinical and experimental work one can also say that in nitrogen mustard there is available a chemical tool by which one can obtain in Hodgkin's disease and certain varieties of lymphosarcomas, results just as good but not superior to X-ray.

Hodgkin's disease was reported to have been cured by splenectomy first and nitrogen mustard subsequently.

Urethane has also been reported to have given relief in bronchogenic carcinoma.

At this stage one earnestly hopes for newer compounds with safety and better results and may it be said that CHEMISTS are not unequal to this task of controlling malignant diseases by chemotherapy.

VIII. ANTISEPTICS IN SURGERY

A profound change in the attitude to antiseptics is noticed during the past ten years. About the first world war, the experience with antiseptics in war wounds had made medical men somewhat sceptic as to their utility. This however did not result in abandoning them, for habits and conventions even in the realm of science often die slow. "Pungent smells, bright colours, ceremonial usage, etc., seem to be passports to popularity; even in highly intelligent beings such is the force of an appeal to the senses" said L. P. Garrod (1948)[10] not unfairly.

Penicillin and the sulpha drugs, since 1940 tended to alter the traditional attitude to antiseptics. Domagk the faithful disciple of Ehrlich held that all true chemotherapeutic agents must act only with the active co-operation of living tissue and incapable of *in vitro* action or when applied locally or directly to an infected surface. Laboratory studies of the action of some of the antiseptics have shown that the view of Domagk was not absolute as some of the antiseptics are able to act directly without the active co-operation of body tissue, tissue fluids, etc., (unless it is the limited local tissue) or reticuloendothelial system. The old question presents over again 'can laboratory findings be accepted unquestioningly or serve as guides to clinical practice ; how far do *in vitro* tests run parallel to *in vivo* happenings ?'

Some of the data to be considered in the use of antiseptics are (1) normal skin is a fairly resistent tissue, while abnormal skin or raw skin is fairly readily susceptible to anything, (2) organisms are much more easily killed in a test tube than in an environment of tissue, (3) the action and reaction between an antiseptic and body tissue are practically unknown, if not vague and inconstant.

Varying with different compounds, the antiseptic in use may be activated or inactivated by the tissue and rendered more or less toxic to the tissue than to the organism. Bearing these data in mind, the scope of antiseptics in surgery may be considered under the heads (1) normal or intact skin, (2) recent wound where the aim of prevention is more dominant and (3) established ulcers with definite sepsis.

(1) *Normal or intact skin* :—This in turn raises the query if it is the skin of the patient before operation (occasional use) or the surgeon's skin (frequent use). There are quick acting and slow acting ones. Alcohol in 70 per cent. strength may suffice in most cases for 'gross' disinfection, while 2 per cent. iodine in 70 per cent. alcohol is used for quick and more efficient disinfection. These procedures would apply to the patient's skin but not for the surgeon's hand as repeated use may lead to irritation by iodine.

Domagk, the originator of the sulphonamides, also introduced the so-called 'Cationic detergents' or invert soaps. Zephyran is popular in America while Cetavlon or cetylzephyran ammonium bromide or CTAB is popular in Britain. These compounds reduce surface tension and exert an efficient cleansing action. They are rapidly bactericidal, acting particularly against staphylococci. But their action on bacteria is much diminished in the presence of tissue fluids and despite their non-irritant nature can cause deleterious action on phagocytes and tissue cells.

(2) *Recent wounds* :—As raw area or exposed tissue is more susceptible than intact skin to the action of an antiseptic, the consideration that should weigh here is 'What is the limit of this tissue damage to act as a barrier to the use of antiseptics ?' If all pathogenic organisms could be killed by an

application of a disinfectant which also damages to some extent the tissue, is the price too heavy ? One is here reminded of the old practice of cauterising any wound with carbolic acid, particularly dogbite, when the antiseptic killed the organism and the tissue surrounding. Nevertheless it is the path of reason to use an antiseptic which has in Ehrlich's parlance minimum organotrophic and maximum parasitotrophic action.

Cetavlon or organic detergent could be used for a recent lacerated wound despite its slightly deleterious action on raw area.

Dusting powders consisting of sulphathiazole and acridin or penicillin have been used. Flavzole or two parts of proflavine and 98 parts of sulphathiazole is popular with some. A deep penetrating wound cannot be treated with this compound as systemic sterilisation is there indicated. Calcium penicillin is often combined with sulphathiazole for recent wounds. This preparation is also useful as a snuff. Penicillin being readily absorbed has evanescent effect when intended for local use. Some pharmacologists hold the view that more than one antiseptic should not be used in any single case. Mixing up of antiseptic tends to introduce the element of incompatibility, to confuse the interpretation and to increase the chances of toxic manifestations. Sulphonamide sensitisation when used as skin disinfectant has frequently been reported. Some hold the view that in sulphathiazole-penicillin or sulphathiazole-proflavine combinations, the sulpha compound merely serves as a vehicle or a diluvent and the main antiseptic is the other partner. The new British Pharmacopœia, introducing several preparations of penicillin for external use seems to advocate penicillin as the choice for recent wounds.

The Council of Pharmacy and Chemistry of the American Medical Association has been lately concerned over the utility of organomercurial antiseptics like mercurochrome, merthiolate, etc. The study of these compounds has revealed that variation in technique, differences in test organisms and differences in criteria of effectiveness had led to different conclusions. In vitro, experiments may not often give a correct idea of their utility.

Recently a new plastic material, a Nylon derivative has been recommended as a safe antiseptic dressing obviating the necessity for gauze, lint, cotton dressings and bandaging. This new plastic is in the form of a transparent film which is tough and can be sterilised at 150 deg. C. It is soluble in 80 per cent. alcohol but not in the usual industrial solvents. Its great property is that it permits evaporation of water so that no perspiration collects underneath. It is also an efficient antiseptic. The practical uses of this new nylon derivative are its protective action on the normal skin, easy application in that the doctor can study the healing process through the transparent covering without having to change the dressings and its efficient antiseptic action.

(3) *Established ulcer with definite sepsis* :—Here the main factor for consideration is if local or systemic treatment is to be undertaken. Presence of pus and disintegrating matter introduce two elements, *i.e.*, the effect of these on antiseptic and *vice versa* and the nature of the infecting agent. The sulpha drugs are relatively ineffective in an environment of pus, barring marfanil which is also effective against *claustridium welchii.* Susceptibility of organism varies with antiseptics. It is of interest that granulation tissue bathed in pus is resistent to the action of many antiseptics. The slowly dissolving powders exert a prolonged action ; proflavine or amino-acridine powders are effective for this reason. But the introduction of penicillin has changed the outlook favourably. "What can be done with other antiseptics can be done with penicillin appreciably well, more often sooner and with more uniformly good results."

For Gram negative infections due to coliform organisms, pyocyaneus, proteus, etc., penicillin, acridine and tyrothricin are not of much value. Some claim better results with a spray of streptomycin while others prefer marfanil.

Recently the diamidine derivatives *i.e.*, dibromo propamidine and iodohexamidine when used as a cream with castor oil or carbowax propylene glycol or as mere powder were found more effective against Gram negative bacilli of pyocyaneus and B coli group. They promise to be of value in appendicular abscess and resulting peritonitis.

Surgeons as a class, it is believed, are beginning to think that aseptic precautions and antiseptics have been overemphasised since Lord Lister though Lister did not intend to make a fetish of sepsis when he pointed to its place in surgery.

(*To be continued.*)

ANKYLOSTOMIASIS AS IT FACES THE PRACTITIONER *

J. C. Patel †

I consider it a privilege to address you today. I have chosen the subject of ankylostoma for to-day's talk as I was told that it is widely prevalent in the District and is responsible for the considerable ill health amongst the population. I shall consider those aspects of ankylostomiasis which confront you in your daily practice.

SYMPTOMATOLOGY

Manifestations of hookworm infection are protean and baffle the uninitiated. The parasitic infections contrary to most bacterial infections such as diphtheria, typhoid fever, etc., are generally characterised by what may be called ' silent lesions.' They are slow in development and consequently when manifested, as a rule, have no definite clear cut symptoms. Such symptoms as do appear are often extremely confusing and are likely to manifest themselves long after infestation has occurred. It is obvious, therefore, that the clinical diagnosis of parasitisms is, as a rule, neither accurate nor timely. Compared to the difficulty of clinical diagnosis the laboratory diagnosis is simple and accurate.

Clinical symptoms can be considered in two ways.

(1) Symptoms produced by the worm during the course of infection of the body and during the stay or (2) consideration of the symptoms, as it effects system by system, regardless of the stage or severity of the infection.

(1) Symptoms of ankylostoma infection as it travels through the body.

The skin route of the infection was discovered by Looss[6] in 1898. Symptoms of invasion are on the skin (ground itch, water itch, pani ghao); the point of entrance of a larva may or may not show an irritating pimple very much like an insect bite. When the larva enters through the hair follicle there may be no pimple. Larva may be contaminated with bacteria which may add septic infection, and then lesion at the point of penetration may be a papule, vesicle or pustule. The surrounding parts or even the whole limb may become inflamed when many larvæ penetrate at one time. The first symptom of a true ground itch is an itching, usually between the toes. This becomes more and more intense, till it is excrutiating. Children often cry at night because of this pain during an attack. Itching begins immediately after wading through mud, there is local small hyperemia, and a macular rash which develops into macules, papules and vesicles. This later become confluent and produce blisters. The condition may last for a couple of weeks or may last several weeks, may involve a small area, may cover both feet and the patient may be unable to walk about for the time being. The infection, even though it is the commonest site, may not be confined to feet. It may occur on buttocks, forearm or knees whichever may have come in contact with mud.

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*Based on a lecture delivered before the Nadiad Branch of Indian Medical Association on 26th December, 1948.

† K. E. M. Hospital, Bombay.

The extent to which a history of ground itch is obtainable in hookworm infection is very variable. In Darjeeling tea garden coolies, it is common and it is absent in Egypt.

Lymphatic glands may be enlarged, painful and tender in a severe case of ground itch. When the larvæ reach the lungs symptoms like cough and expectoration, sometimes with bloody sputum are apt to follow severe ground itch. Cough might vary from mild to severe paroxysmal, persisting for two to three weeks. Hoarseness and aphonia may occur. Dyphagia due to larvæ may often be next and later epigastric pain, vomiting diarrhœa and gross intestinal hæmorrhage may be other symptoms. After this the infection may remain silent or may produce symptoms of anæmia of insidious origin, accompanied by weariness, listlessness and indigestion. The anæmia, a progressive one, which in uncomplicated cases, is not associated with wasting. If the progress of a case be unchecked, serious effusions and fatty degeneration of the heart ensue and death may occur from syncope or from intercurrent complication.

(2) Symptoms as considered system by system, may be described as follows :—

General.—In those living in an endemic area, the symptoms might be an undue tendency to fatigue, lassitude and digestive disturbances, palpitations, tinnitus, vertigo dimness of sight, mental apathy and depression, liability to syncope. Temperature is usually subnormal, but low temperature, or fever of an irregular intermittent kind may occur. Generalised anasarca occurs in late stages.

Alimentary System.—Pain, dysphagia and uneasiness in the epigastric region are some of the early symptoms after the invasion. This may be increased by pressure and may for the time being be relieved by food. The pain is sometimes mistaken for that of duodenal ulcer. The stomach is often dilated and gastric juice may show hyperacidity. It has been suggested that the desire to neutralise this acidity with an alkali is the explanation of the desire for alkali containing earth (geophagy) on the part of dirt eaters. Taste may be perverted. As anæmia increases the acidity diminishes and later achlorhydria may occur. Appetite may be ravenous at some stage but often defective. Constipation is the rule, but bowel irregularity may occur. Diarrhœa and stool with blood and mucus (helminthic dysentery) has been known to occur. Colic, flatulence may occur. Patients may have pot bellies and in extreme cases may have ascites. Liver and spleen may or may not be enlarged.

Skin Manifestations.—Dermatitis on the toes and feet, urticarial rash may occur all over the body. Skin is often dry or pale earthy colour. Brown patches may be present on the face. The hair is dry and scanty, or absent in pubic and beard regions; œdema, especially of ankles or feet is common.

Circulatory System.—Symptoms are usually due to anæmia. Attacks of palpitation are early and marked. The heart is dilated to the right. Pulsation of neck veins is common. Hæmic murmur is present in advanced stage. The pulse is fast, blood pressure is low. A high pulse pressure is common in severe cases.

Respiratory System.—Symptoms of catarrh, hoarseness, aphonia, cough, bronchitis, paroxysmal bronchitis, simulating bronchial asthma and tropical eosinophilia occur during the passage of larvæ through the pulmonary alveoli. Breathlessness on exertion is the most common respiratory symptom when anæmia develops.

Nervous Systems.—Physical and mental tiredness is a common symptom. Patients have very little energy or initiative and are often considered stupid and lazy. Hypochondriasis is at times noted and some severe cases become melancholic. Tingling and numbness, dead limbs, are also complained of by ankylostoma patients. Deeps jerks are diminished. Mental retardness in children is frequently observed.

Kidney.—Hæmaturia has been reported. Nephrosis has been associated with hookworm infection which has cleared up with the treatment of the worms. In this condition reversal of albumin-globulin ratio, anæmia, high blood urea, normal blood pressure, casts in the urine and œdema are often present.

Ankylostoma and Children.—The growth of body and mental development are apt to be delayed and stunted. They have pot bellies. There is some belief that after generations of exposure to this infection a certain degree of tolerance is attained.

Ankylostoma and Pregnancy.—Hookworm disease exerts a very deleterious influence on pregnancy and in heavily infected districts it is the most common cause of repeated abortions and miscarriages. There is a very heavy maternal and fœtal mortality. Toxæmias of pregnancy such as pre-eclampsia, eclampsia and nephritic toxæmia occur more frequently in women, harbouring worms.

Character of Anæmia.—The anæmia is often the most prominent symptom in hookworm infection and is generally recognised first by the pallor of mucous membranes. It is accompanied by usual symptoms of weakness, fatigue, palpitations and dyspnœa. The children are often physically and mentally backward; puberty may be delayed. Often the abdomen is distended and rapidly developing asthenia may occur. Anæmia may reach the most severe stages quickly in some, but in others very slowly. It usually, appears 10-20 weeks after infection. Different hypothesis have been offered to explain the pathogenesis of hookworm anæmia. They are :—(1) Absorption of toxin through ulcerations resulting from the attachment of worms. (2) Direct innoculation of anæmia-producing organism by infective larvæ. (3) Trauma and secondary bacterial invasion. (4) Disturbances of gastric function. (5) Toxin injuring organs of hæmopoesis, Toxins are secreted by adult worm and toxins may be generated by the activity or death of larvæ. (6) Blood loss due to (a) blood sucking activities; (b) bleeding from wounds; (c) depletion of hæmopoetic substances. (7) Combination of 5 and 6.

De Langen[2] (1922) was the first who attributed this anæmia to a toxin which depresses the synthesis of hæmoglobin. Ashford[1] (1904) held the view for a long time that hæmolysin were chiefly responsible for hookworm anæmia. Experiments were planned and carried out at Johns Hopkins Hospital[3] to answer the following questions:—

(1) Can an infestation of worms remove enough blood from its hosts to account for the observed degree of anæmia in terms of blood loss? In other words, is it necessary to postulate some additional causal factor? (2) What is the type of anæmia produced by hookworm and does the type suggest its ætiology? (3) How does the picture of a developing hookworm anæmia compare to that of an anæmia which is being produced by artificial hæmorrhage. (4) Does hookworm anæmia respond to iron therapy as do hæmorrhagic anæmias, or is it refractory because of intoxicated hæmopoesis? (5) Is it a self-compensative anæmia, or is there evidence of failure of hæmopoetic centres?

Experiments were done on dogs who harbour ankylostoma caninum which is a violent blood sucker to provide for the answers to the above and anæmia was produced by repeated bleeding in a group of dogs. These anæmias were compared in all aspects.

It is found that the adult worm feed largely in the blood lying in the mucosa of the intestines. Each worm is roughly estimated to draw daily by Nishi 0.7 c.c., by Wells 0.84 c.c., Sai Ryo 0.37 c.c., Faust 0.67 c.c. One hundred worms will draw anything between 37 c.c. to 84 c.c. of blood per day[10]. Loss occurs not only because of blood sucking activity of the worms, but also because the loss may continue from the site of the bite for a considerable period after the worm release its hold on the mucosa and moves to another spot. It seems obvious that a continual loss of the blood is the cause of anæmia. However, because in some cases the anæmia seems to be too great in proportion to the number of parasites present some observers insist that there must be another factor in its production.

Answering those above questions, Foster and Landsberg[3] at Johns Hopkins Hospital found that anæmia of hookworm disease is a typical 'microcytic hypochromic' type, which is the type of anæmia clinically associated with chronic hæmorrhage. They both responded equally to iron therapy. Anæmia associated with hookworm infestation in dogs was not due to hæmopoetic failure, thus precluding the necessity of existence of toxin.

Foster and Landsberg[3] have found that anæmia of hookworm disease in dogs is typically characterised by microcytosis and hypochromia. Anæmia in dogs due to hookworm was compensated in some cases. It is commonly observed however, that light worm burdens usually don't produce either clinical disease or a pathological blood picture and this has been usually explained on the basis of compensation. Furthermore, observations like those of Smillae[9] (1922) in Brazil and Rhodes *et al.*[8] (1934) in Porto Rico have shown that occasionally individuals may harbour large worm burdens and yet show nearly normal hæmoglobin levels. The fact that the phenomenon of compensation, as observed in dogs has appeared to be associated with the development of resistance to infection makes it difficult to offer more than presumptive evidence that a similar or related phenomenon of compensation exists in the anæmia of human hookworm disease.

Rhodes *et al.*[8] (1934) in a study of 83 patients with hookworm anæmia in Porto Rico thought that the anæmia was due mainly to insufficient blood production as a result of a deficiency of available iron and other hæmopoetic substances like animal proteins, minerals and vitamins in the body. This deficiency is produced by multiple factors, defective diets or indirectly by gastro-intestinal changes or by blood loss due to hookworm. Clinical diagnosis of ankylostome is most difficult to make and notoriously, uncertain and physicians of experience have misjudged the incidence by a wide margin. The treatment of ankylostoma anæmia is to make up the deficiency of iron and other substances mentioned above besides deworming.

Laboratory diagnosis.—Definite diagnosis can be made by finding hookworm ova in the fæces, (2) larvæ and (3) adult worm. Charcot-Leyden crystals are often present in hookworm stools. Eosinophilia (10 per cent. to 20 per cent. occasionally higher) is usually present, but is inconstant. Sai Ryo[9] (1937) in his 3 experimental volunteers found eosinophilia present on the third day after the infection, it reached its maximum height in sixth and seventh week and decreased after fifteenth week. The percentage of hæmoglobin and the eosinophilia decrease concurrently and may be absent in severe cases when hæmoglobin has fallen below 30 per cent. Total leucocytes vary from 2,500 to 10,000 per c.mm. and will fall in the later stages. As regards gastric secretion, the quantity of free acid varies with the state of blood. In severely anæmic persons there may be hypochlorhydria or achlorhydria.

TREATMENT

Prophylactic treatment.—Two general methods of controlling hookworm infections are known, one method consists in prevention of additional infection, the other, in the treatment of existing infection. The first method resolves itself largely into improvement of sanitary conditions with consequent elimination of soil pollution while the latter, to be effective, necessitates the use of mass treatment, *i.e.*, wholesale treatment of entire communities at a time, usually without individual diagnosis where the percentage of infected individuals is known to be very high. The first method is universally recognised as the one of choice and the only method which can be depended upon to bring permanent relief. But simple as it seems in theory, it is not easy matter to induce hundreds of millions of people to change habits which are hardened by countless centuries of use and to adopt habits which are not only unfamiliar but usually appear obnoxious. Consequently, sanitary reforms require labour, patience and time. Except on estates, where force can be used, no radical improvement in sanitary conditions over a considerable area can be expected in a short time. The treatment method on the other hand brings immediate relief to the individuals involved, but to have any prolonged effect, it must be applied to the majority of groups all at once in the forms of a mass treatment and must be repeated at intervals. The benefits of mass treatment are well known on estates or tea plantations.

Hookworm disease tends to disappear in towns and cities where there is an efficient sewage system. The disease is one of the most conspicuous examples of soil pollution disease. Fæcal contamination of the soil and water must, therefore be prevented. Conservancy system should be such that eggs and larvæ are destroyed. Chinese method of storing the fæces is the best. The water supply should also be carefully guarded from all possible sources of fæcal contamination.

Several mass treatments spaced a few months apart and accompanied by the establishment and use of the appropriate type of sanitary latrines are needed to reduce hookworm infection in the community to a clinically negligible status. Methods for determining the percentage of infection in a given area are twofold, involving (i) the infection in human population and (ii) the infection in the soil. The former is determined fairly accurately by examination of fæces of a representative group of the area. The latter is determined by using the apparatus for isolation of the infective larvæ from the soil. I hope doctors of this place will make an attempt to find out the incidence of infection in the district.

Geographical distribution of human hookworms is governed by two critical factors (i) the areas of land in which climatic conditions are favourable for the growth of the free-living phase of the life cycle of the hookworm in the soil and (ii) the actual incidence of infection of several species mostly two, in indigenous populations.

In India both worms exist. In Southern India and in Ceylon, Necator Americanus is predominant infection, but Ankylostoma duodenale has been introduced by Chinese. In Northern India Necator is only found in Darjeeling area, otherwise Ankylostoma duodenale is the more common infection. In Central India both are prevalent. Due to migrations of populations, the kind of worm is carried from place to place and the old world worm is found in the new world and *vice versa.*

"HOOKWORM THERAPY"

The ideal drug for the treatment of hookworm disease should have the following qualifications. (1) Single treatment should remove all the hookworms harboured. (2) It should remove other common intestinal parasites such as round worm, whipworm and tænia. (3) It must be non-toxic to the patients. (4) It must be easy to administer. (5) The cost of the drug must be cheap.

We will consider the following five drugs in the treatment of hookworm:—(1) Thymol, (2) Oil of Chenopodium, (3) Carbon tetrachloride, (4) Tetrachlorethylene, (5) Hexyl resorcinol.

(1) Thymol was used by Bozzolo in 1879 in the treatment of hookworm. Maximum dose should not exceed 60 grs. in an adult and 30 grs. in a preg nant woman. It is usually given in 2—3 divided doses of 15, 20, or 30 grs. each at intervals of 1 to 2 hours followed by a strong saline purgative.

The patient is given a light meal and one ounce of saturated solution of magnesium or sodium sulphate the night before. The following morning, on a hungry stomach, 30 grains of powdered thymol are given in capsules at 8-30 a.m. and at 10 a.m. At 11 a.m. 1 ounce of saturated solution of magnesium sulphate is given. No food is allowed till after bowels have moved. The patient remains in bed and should use a bed pan. The drug should not be repeated for a week.

Clayton Lane[5] regards it as the best anthelmintic. It has no effect on other worms. Fats and alcohol increase the toxic effects and so they should be avoided. Toxic effects are like those of carbolic acid poisoning. It should be given with caution when there is anæmia, nephritis, advanced cardiac disease, pregnancy and debility due to old age. It has been generally superseded by anthelmintics which are more efficient or which have greater margin of safety.

2. *Chenopodium.*—American Indians used it before Columbus discovered America. But it was not popular because of toxic effects. During the 1st World War (1914-1918) due to shortage of santonin and thymol, it came in use. It was used in Dutch Indonesia for the first time. It contains 40 to 80 per cent. of ascoridol—an essential oil—which is an active constituent.

It has action on all kinds of intestinal nematodes particularly on ascaris and is as good as santonin. It is less effective against Necator Americanus than carbon tetrachloride, but is about equally affective against ankylostoma duodenale.

Maximum dose is 3 ml. given in 3 doses of 1 ml. each at intervals of one hour. The last dose is followed one hour later, by an ounce of concentrated solution of magnesium sulphate.

Chenopodium has a very obnoxious and nauseating taste and is preferred to be given in hard gelatin capsules or with syrup or sugar. Purgative should be given one hour later as the simultaneous administration reduces the anthelmintic efficacy of the drug. Fixed oils like olive oil prevent toxic effect of the drug.

Toxic effects of oil of Chenopodium are :—severe irritation of mucous membrane of gastro-intestinal tract producing nausea, vomiting, abdominal pain and finally paralysis of the gut. Dizziness is always present. Larger dosage or in certain cases of feeling of intoxication, prostration, headache, drowsiness and unconciousness occur. Death occurs in some cases.

It should be given with caution in diseases of heart and kidneys and when hepatic and gastro-intestinal disorders are present.

3. *Carbon tetrachloride.*—Hall[4] (1921) used it on domestic animals in 1921 and brought it to the attention of medical profession for its use in hookworm. The dose is 3 to 4 ml. The drug is preferably given in a capsule. The patient should be prepared before treatment. He should take light supper on the previous evening. With no breakfast on the morning of treatment he is given 3 ml. of the drug. Two hours later he is given a saline purge. The treatment should not be repeated for a week. Contra-indications to this drug are alcoholism, pulmonary or heart complications, nephritis, pyrexia and calcium deficiency. Toxic effects of the drug are a peculiar taste in the mouth, eructations, uncomfortable sensation in mouth diarrhœa, vertigo, headache, somnolence of a temporary nature, drowsiness, sleep with dilatation of pupil, jaundice, hæmaturia, albuminuria, and death.

4. Tetrachlorethylene was recommanded by Hall in 1925, who found it very efficient and essentially non-toxic in removing hookworm in dogs. The dose is 3 ml. to 4 ml. The efficiency of the drug is 95 per cent. The preparation of the patient and method of administration are same as with carbon tetrachloride. The toxic effects are transient giddiness, drowsiness and occasionally irritation of central nervous system. The patient should abstain from taking alcohol or fat for two days preceding the treatment. The drug is two or three times costlier than the carbon tetrachloride. There are no contra-indications. It has less action on ascaris lumbricoides and on the contrary makes them migrate towards stomach and hence they should be removed before the drug is given for hookworm. It is a drug of choice in hookworm infection because of higher efficiency and less toxicity.

5. Hexyl rescorcinol is moderately efficient in eradicating hookworm. The dose is one gramme. The preparation of the patient is to give a saline purge on the night before the day of the treatment. The drug is given on an empty stomach next morning with no food until noon. The purgative is administered next morning. It has a high degree of efficiency against ascaris infection and it is a drug of choice in combined infection of round

worm and hookworm. It must not be chewed and must be given on a fasting stomach.

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SOCIETY PROCEEDINGS

TEACHING PATHOLOGISTS, BOMBAY

The 83rd meeting of the Teaching Pathologists of Bombay was held on Saturday 29th January 1949 at 2-30 p.m. in the Haffkine Institute, Dr. R. M. Wagle took the chair.

Before commencing the proceedings of the meeting Prof. Gharpure proposed a condolence resolution for the sudden and untimely death of Dr. Bhaskar Menon, which was unanimously passed standing. He then gave a brief sketch of Dr. Menon's carrier after his graduation in medicine.

PYROGEN AND ITS PREVENTION

Mr. K. H. Bharucha read a paper on "Pyrogen and its prevention in the preparation of transfusion fluids". The paper began with abstracts of several papers relating to the subject. Rademaker's paper describing a type of still that would give pyrogen-free single distilled water was explained by means of diagrams and discussed. Walter's methods laying stress on thoroughly cleaning all parts of the apparatus used both in the preparation and injection of transfusion fluids were next described and discussed. Mr. Bharucha related the experience of another institution where severe reactions were traced to a new packet of filter paper. Co Tui's work on absorptive filtration a method of removing pyrogen was described and compared with the work of Zittle and of Smith and Pennell. The drawback of the method, namely, the large number of pads required for removing pyrogen from incomplete hydrolysates of proteins was pointed out by means of tables. Other methods of removing pyrogen, namely, by activated charcoal, or boiling with hydrogen peroxide, or by dialysis were reported. Collier's paper on the loss of pyrogenic activity during storage was also discussed. Details of the methods followed at the Haffkine Institute were reported and discussed.

Discussion:—A representative of 'Cipla Laboratories' suggested that pyrogens being carbohydrate in nature may be destroyed by boiling with N/100 hydrochloric acid. The acid may be subsequently neutralized.

Dr. Mrs. Soman reported very severe reactions in her patients after administration of T. A. B. Vaccine and inquired if these reactions were due to pyrogen. Mr. Bharucha, in replying to the first question, doubted if the small quantity of hydrochloric acid suggested would destroy pyrogen and suggested that the treatment would destroy some of the glucose if carried out with glucose saline.

Dr. Wagle, from the chair, in replying to Dr. Mrs. Soman, said that the most virulent strains were selected in the preparation of T. A. B. Vaccine and the reactions might be due to that factor.

Mr. B. V. Patel in replying to the same question suggested that 1 or or 2 c.c. of T. A. B. Vaccine given subcutaneously could not introduce so much pyrogen as to produce reactions.

THIAZOLE DERIVATIVES

Mr. B. V. Patel then read his paper on "Chemotherapeutic activity of Thiazole derivatives". He had studied the chemotherapeutic activity of N^1-methyl-sulphathiazole (I), 2-N^1-sulphanilamid-5-ethylthiazole (II) and 2-N^1 -sulphanilamido-5-isopropylthiazole (III) in experimental streptococcal (Richard's strain of hæmolytic streptococcus) and pneumococcal (Pneumoccoccus type I) infections in mice. In the experiments the mice were given intraperitoneally 0.5 c.c. of 1 in 6 dilution of the 17 hour old culture in case of streptococcal infection and 1 in 2,000 dilution in the case of pneumococcal infection. In the case of streptococcal infection the drug was administered twice a day by mouth for 3 days and the mice were observed for a period of 10 days. In case of pneumococcal infection the mice were fed with drug for a period of 5 days and were observed for 15 days. The drug under test was made into a suspension with tragacanth so that 0.5 c.c. of the suspension contained 20 mg. For comparison tests were also put up with sulphathiazole and in every case the average survival time was calculated. None of the drugs tested was found to be superior to sulphathiazole.

In the experiments with streptococcal infection it was observed that the blood smear from tail vein and heart blood culture of mice surviving the observation period of 10 days showed presence of hæmolytic streptococcus. The blood smears on detailed microscopic examination showed the organisms to have undergone some morphologic change; a swollen form was often seen and the characteristic chain formation was not seen; usually they were single or in groups of two or three. These mice later died of streptococcal septicæmia, after 70-90 days. This observation threw some light on the mode of action of sulpha drugs and is still under investigation.

Dr. P. M. Wagle asked whether post-mortem was done and whether any macroscopic changes were observed in spleen, lungs, liver etc. as seen in case of plague infected mice that survived after treatment with sulphathiazole or sulphadiazine.

Dr. V. R. Khanolkar enquired whether the blood smears were examined during the course of treatment and the period of observation to see whether the organisms were present or not.

Dr. Bhatacharjee said that pharmacological study meant study of the absorption, excretion and toxicity both acute and chronic. He wanted to know whether the number of organism in each infective dose was determined.

Mr. Patel in reply said that the post-mortem examination was done in every case and no abscesses or any other morphological changes in the organisms were observed. The blood smear during the course of treatment and period of observation were not examined. The absorption, excretion, and toxicity of these drugs had been studied but count of organisms was not taken as the control mice always died within 48 hours.

ENTERIC FEVER IN BOMBAY

Dr. B. G. Modi read a paper on "Enteric fever in Bombay". In his preliminary remarks he explained how he was able to investigate the cases of typhoid and paratyphoid with the help of Typhoid Unit Scheme sanctioned by the Government. He described the method of collection of blood for laboratory investigation. 424 samples of blood were examined and 112 cultures of B. typhosus and 20 of B. para. A were isolated. By serological and cultural examinations 223 cases were diagnosed as suffering from typhoid and paratyphoid infection. Only 156 cases could be diagnosed serologically.

The comparative value of whole-blood cultures and clot-cultures was studied in a certain number of cases and it was realized that more clot-cultures were positive than blood cultures and the former appeared also earlier. The collective data of clot cultures for a period of 10 years at this Institute showed that the ratio of typhoid to para. A cultures isolated was 9 : 1. No paratyphoid B culture was isolated during those years. Para. C and other salmonella cultures were isolated occasionally.

Out of 132 bacteriologically proved enteric cases 112 were selected for study in the light of laboratory and clinical findings. Widal reaction was negative in 56 per cent. of cases although blood was collected after 10th day of fever; thus the value of negative widal tests with positive blood or clot culture was stressed.

The leukopenia in enteric fever so prominently stressed in text books was particularly investigated in these cases and it was observed that 57 out of 93 cases did not show any evidence of leukopenia, total W. B. C.

count being between 5000 to 11000 per cu. mm. ; the average differential count figures showed relative lymphocytosis. 50% of cases gave history of intermittent pyrexia. The presenting symptoms were continuous fever or fever with rigors (56 per cent.), cough (17 per cent.) fever with diarrhoea (15 per cent.), fever with hiccough (4 per cent.), and fever with blood in stool (4 per cent.). Temperature came to normal between 14-21 days in 10 cases, between 22-28 days in 29 cases between 29-55 days in 13 cases, between 36-42 days in 8 cases and beyond 42 days in 17 cases. Mortality rate was 16 per cent. Incidence of complications was 50 per cent and diarrhoea, distension and toxæmia were the most common. In the discussion that followed Dr. P. M. Wagle referring to the high per centage of negative widals, wanted to know what 'O' antigen was being used for the Widal tests, as certain antigens were more sensitive than others. He also stated that he found more blood cultures positive than clot cultures in his series of cases in 1938-1939. Dr. Banker agreed to the ratio of isolations of B. typhosus to B. para. A cultures as 9:1 ; however, he laid stress on the study of the strains of para. A isolated which in certain cases may help to trace the source of original infection. His mortality figures were 25 per cent. He suggested that cultures showing no growth after 5 days should not be discarded as negative as he had found them positive after 10-12 days. Dr. Mrs. Soman, in her group of fatal and recovered cases found that 'O' agglutination did not show any suggestive prognostic difference and the cases either fatal during early days of illness or very late in the course of disease and she wanted to know whether diet had anything to do with those late deaths. She also wanted to know what would be the normal average figures for total W. B. C. and D. C. in Indian children as the English text books usually showed higher figures. Major Gharpure wanted to know whether reports of positive cases were submitted to the Municipality.

Dr. Modi in reply to Dr. Wagle's question said that 'O' antigens used at present were agar suspensions from Typh. O 901 strain and carbolised. Regarding Dr. Mrs. Soman's question, the figures of Total W. B. C. and D. C. in normal Indian children he had no such data to supply. To Prof. Gharpure's question, Dr. Modi informed that all cases whether negative or positive were reported to Executive Health Officer.

A section showing Rhinosporidiosis from the pharyngeal wall, mistaken for adenoids by the Surgeon was put up for demonstration.

The 84th Meeting of the Teaching Pathologists was held on Saturday the 26th February 1949 at the Gordhandas Sunderdas Medical College, Bombay. Dr. Y. M. Bhende was in the chair.

1. SEROLOGICAL TESTS IN THE DIAGNOSIS OF SMALL POX : P. J. BADSHAW.

The various serological tests available were: (1) viricidal property of the serum (2) flocculation test and (3) complement-fixation test. The first one was not a practical procedure as a routine diagnostic test because of the technical difficulties and the long time required to read the results. The two, latter, were simple to carry out and the results were obtainable within a few hours. The specificity of the flocculation and the complement-fixation tests, though challenged by some, had been amply demonstrated.

The results of Paschen smear method of diagnosing variola-vaccinia in a series of 52 cases of fever with generalised rash had already been discussed in a previous meeting.[1] The present study aimed at confirmation of the results of the Paschen test by serological examination. Flocculation Test :—For this test positive control antigen was prepared from variola crusts and raw vaccine pulp ; negative control antigen was prepared from varicella crusts. The unknown antigen was prepared from crusts and vesicular or pustular fluids from patients suspected suffering from variola. Two types of antigens were used : (i) crude antigen and (ii) purified antigen, obtained by differential centrifugalisation. Essentially, they consisted of a suspension of the elementary bodies. High titre immune serum was obtained by inoculating rabbits with pooled variola crust antigen. The flocculation test was utilised both to demonstrate the presence of specific antigen in the lesions and specific immune bodies in the patient's serum. The technique of preparation of the antigens and the immune serum and the procedure of the test were described in detail.

Complement Fixation Test :—The antigens were the same as in the previous test. Immune serum again came from the rabbit. The complement was guinea-pig serum. Positive and negative control antigens were the same as in the flocculation test. Positive control serum was the immunised rabbit serum ; negative control serum was the normal rabbit serum. The technique of the test was discussed in detail. This test, as in the previous case was utilised to verify the presence of specific antigen in the lesion or the specific antibody in the patient's serum.

The material studied for the two tests was obtained from 47 cases (variola : 43 and varicella : 4) and consisted of sera from 23 cases, crusts from 36 cases, and, vesicular and or pustular fluids from 7 cases. The results were as follows :—Of 21 sera from cases of variola (final diagnosis) 6 gave positive flocculation and complement-fixation tests with the antigen prepared from crusts. In 1 case only the complement-fixation test was positive. In every case the complement-fixing titre was found higher than the flocculating one. Using the vaccinia antigen only 3 of the 7 were positive by both tests and the titres were low. Using positive immune rabbit serum, 23 out of 32 variola crusts examined showed the presence of specific antigen by the flocculation test. One of the varicella crusts gave a false positive reaction. Using the immune rabbit serum all the 5 vesicular or pustular fluids from variola cases gave positive flocculation and complement-fixation reactions. One fluid from a varicella case gave a false positive complement-fixation test. In 15 cases an attempt was made to demonstrate the presence of specific antigen in the material from the lesions and the specific antibody in the serum; in 9 cases the specific antigen could be detected and in only 3 the specific antibody. In all the last 3 cases the tests for antigen were positive. Combining all the figures it was found that of the 43 cases of variola in 30 the serological tests (whether with the material from lesions or with the serum) were positive; 26 out of 35 specimens of material from the lesions showed the presence of the specific antigen; and, 7 of the 21 sera gave positive tests. Results, with the crusts or the vesicular and pustular fluids were better than with the serum of the patient. The poor results with the latter were attributed to two factors (i) sera were collected from different cases at a varying interval during their course (ii) prolonged storage due to technical difficulties. The present study also showed that 'variola' antigen was a better reagent than 'vaccinia' antigen for serological diagnosis. The two false positive reactions with varicella antigen were explained as probably due to contaminating bacterial antigens since pure elementary body suspensions were not used in the tests. Comparing the results of Paschen smear method with those of the serological tests it was concluded that the former outstripped the latter in accuracy, speed and simplicity of technique.

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[1] Badshaw, P. J. : A Simple Laboratory Test for the Early Diagnosis of Variola, Ind. Jour. Med. Sci. 2 : 248-250, 1948.

Discussion:—Dr. P. V. Gharpure enquired if a special attempt was made in this study to find out the effects of storage on the activity of the sera. In his experience stored sera showed gradual loss of activity in a definite fashion as far as the different antigen-antibody reactions were concerned.

Dr. V. R. Khanolkar suggested that the sera could be lyophilised and stored without any loss of their activity.

Dr. Badshaw, in reply, said that no special attempt was made to study the effect of storage on sera, but, it was observed incidentally that those sera which had been stored for a few months only yielded more positive results than those that had been kept over a year.

2. THE SEMINAL FLUID IN CASES OF STERILITY :—K. N. VAIDYA.

This was a study of 50 cases. Forty-eight specimens of semen came from patients referred for a childless marriage; 1 specimen was from a bachelor who wanted to know if he was potent and 1 from a person whose wife complained of burning sensation in the vagina after the discharge of semen.

Of the three methods for collection of semen—by masturbation, by coitus interruptus, and, by intercourse with a condom—the first one was to be preferred because it was simple and the specimen could be obtained fresh and without contamination. The sample was examined immediately. The examination consisted of noting the (i) volume (ii) viscosity (iii) sperm count (iv) motility of the sperms—immediately and after 6 to 8 hours (v) presence of abnormal sperms (vi) presence of pus cells and (vii) presence of organisms.

The results were as follows :—The volume varied from 0.6 ml. to 6.0 ml. The volume was no criterion of potency to fertilise; in 1 case with a volume of 6 ml. the sperm count was poor and all the sperm were non-motile. Viscosity of the fluid was of value as it had been claimed that increased viscosity reduced the chances of spermatozoa reaching the cervical canal. In 1 case even after 12 hours at the room temperature the semen failed to liquify; the microscopic examination of this specimen showed that the sperms had restricted motility. Motility of the sperms was studied in a wet-film preparation and an attempt was made to determine (i) percentage of active sperms (ii) type of motility and (iii) duration of motility. This, together with the sperm count gave good indication of the potency of the semen and was the most important part of the examination. A sperm count of 70 millions per ml. or above was considered 'normal', a count between 10 to 70 million was considered 'moderate', and, a count below 10 million per ml. as 'poor'. Of the 50 patients, 14 had aspermia (no sperms even in the centrifuged deposit); 16 had a count less than 10 million per ml. and of these in 2 the motility was 'good', in 7 'fair', and, in 7 'bad'; 16 had a count between 10 and 70 million per ml. and the motility was 'good' in 10, 'fair' in 3, and, 'bad' in 3; 4 had a count of more than 70 million per ml. and the motility was good in all. Only a single specimen was examined in the majority of the cases. The morphology of the sperms was studied in a smear stained by Gram's method. In 1 case about 28 per cent. of the sperms were abnormal. Pus cells, if present in large numbers, were of significance; in 1 case the semen was full of pus cells and this patient was a case of old gonorrhea. In this last case, a large number of Gram-negative bacilli were also found in the smear. There was not a single case which showed gonococci.

Discussion :—Dr. V. R. Khanolkar enquired whether the sperm count showed any seasonal variation.

Dr. M. G. Pradhan said that in his opinion coitus interruptus was the method of choice as masturbation did not always succeed in obtaining a specimen.

Dr. Vaidya in reply, said that though he had a few occasions to repeat the sperm count on the same patient he had not made any observations on seasonal variations.

3. STRUMA OVARII: REPORT OF 2 CASES: S. N. KOTHARE.

The term "Struma ovarii" was applied by some to an ovarian neoplasm in which no other element except thyroid tissue was present. Others meant by it a teratoma in which there was one-sided development of thyroid tissue.

The first case was that of a female aged 45 years admitted for pain in the hypogastrium and general weakness of 1 year's duration. Examination showed a lump in the hypogastrium, intra-abdominal, measuring 10 cm. in diameter, and, in connection with the uterine adnexa. There was ascites. The resected lump measured 10 x 7 x 5 cms. and was well capsulated. Cut surface was solid in some portions and cystic in other portions. Histological examination showed abundant thyroid tissue in the form of acini containing colloid and lined by cuboidal epithelium. There was no evidence of malignancy and no teratomatous elements could be detected.

In the second case, the neoplasm was an incidental finding during an autopsy on a case of leprosy. This neoplasm measured 6 x 3 x 3 cms. Cut surface showed a large cyst containing sebaceous material and hair. Histological sections showed abundant thyroid tissue in the walls of the cyst in the form of acini full of colloid and lined by cuboidal epithelium. In between could be made out other teratomatous elements like skin with its appendages and cartilage.

It was pointed out that struma ovarii was a rare neoplams of the ovary. Upto 1940 only 152 cases had been described[2]. Some cases were associated with dermoids, some with serous or pseudomucinous cystadenomas and others showed only thyroid tissue. Cases showing symptoms and signs of hyperthyroidism had been reported and malignant change had also been recorded in the neoplasm. Most authorities believed that struma ovarii originated in an ovarian teratoma ; some had suggested that it arose from the downgrowth of the surface epithelium of the ovary.

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[2] Smith, F. G.: Pathology and Physiology of Struma Ovarii, Arch. Surg. **53**: 603, 1946.

Discussion :—Dr. P. V. Gharpure enquired if there was any hydrothorax in the 1st case. He also wanted to know the condition of the thyroid in the second case which came for autopsy.

Dr. Kothare in reply, said that no hydrothorax was detected in the first case even after screening the chest.

Dr. L. Monteiro who had performed the autopsy on the 2nd case said that nothing abnormal was detected in the thyroid.

CURRENT MEDICAL LITERATURE

MEDICINE

INTRAVENOUS TREATMENT OF ANAEMIA WITH AN IRON-SUCROSE PREPARATION. SLACK, H. G. B. and WILKINSON, J. F. Lancet I : 11-14, 1949, 1 graph, 2 tables, 8 refs.

It is well known that few patients of iron deficiency of anæmia do not respond to large doses of both Ferrous and Ferric Iron by mouth. Some do not tolerate the drug. It is in these patients that parenteral administration of iron is useful. During the past, injections of iron has either proved too painful, or have produced severe heavy metal-intoxication. Authors have found the preparation of saccharide (2 per cent. iron) useful in treatment of iron deficiency anæmia. This iron-sucrose preparation has been given intravenously in repeated doses for therapeutic or experimental purposes to over 120 people. Out of these 60 patients had iron deficiency anæmia. About a third of these have been treated with a substance prepared by them, (the method is described in detail in the text) and the remainder had another form of iron sucrose preparation " Ferrivenin " supplied by Bengers Ltd. There have been no detectable difference in tolerance or response of either of these two preparations. The drug was given in a dosage of 25 mg. on the first day, 50 mg. on the second day ; 100 mg. on the third and 200 mg. on the 4th and subsequent days. Occasionally the patient had 200 mg. twice daily with an interval of six hours. The total dose was calculated to be within the deficit as arrived at by the hæmoglobin estimation. Injection was given intravenously with an all glass syringe at the rate of 2 ml. a minute.

In 700 injections, thrombosis occurred in four veins. Few people developed mild iron intoxication. Treatment was usually completed in 10 out-patients visits. The patients do not require rest after the injection. Out of these 60 patients, 10 had proved refractory to full doses of iron by mouth over long periods. In almost all patients there was a rapid and complete amelioration of such symptoms of anæmia. Hæmotological and clinical responses were as dramatic as those obtained when patients with pernicious anæmia in relapse received adequate dosage of the potent intramuscular liver extract. Reticulocyte peak of 10—18 per cent. developed in 7—10 days after the first injection. Earliest clinical improvement was return of appetite, 48—72 hours from the beginning of the treatment. Utilisation of intravenous iron-sucrose preparation appears to be nearly 100 per cent. Utilisation however is seriously interfered with in cases of chronic infection. Authors conclude that this iron sucrose preparation is an effective, safe and easily administered form of iron of great value in the treatment of iron deficiency anæmia that has proved refractory to iron given by mouth, or to patients who do not tolerate iron by mouth in adequate dosage. The calculated iron deficit given in this manner is utilised almost quantitatively and does not appear to require the supplementary trace elements ascorbic acid, or folic acid.

J. C. PATEL.

INTRAVENOUS IRON IN THE TREATMENT OF ANÆMIA OF PREGNANCY. GORAN, A. D. T. and SCOTT JEAN M. Lancet I : 14-16, 1949, 3 fig. 7 ref.

The authors recall difficulties in treating the common iron-defficiency anæmia of pregnancy by oral method ; namely : lack of time, intolerance and lack of response to the therapy. The anæmia is urgent as it appears in the latter months of pregnancy, and transfusion is the only means of treatment. They have treated 25 cases with ferivenin of Bengers Ltd. and compare the results shown by patients given iron by mouth. The dose of ferivenin was 30 mg. of elemental iron on the first day, 60 mg. on the second day, and 100 mg. thereafter for the first week. At the end of the week, injections of 100 mg. were given on alternate days. The response was uniformly good. There was reticulocytosis in the majority of them. The highest was 16 per cent. There was clinical improvement in all. Response of rise of hæmoglobin was delayed in few cases. They found the solution irritable to the vessel wall, and rapid injection causes an immediate venospasm, but, if the solution is given slowly, thrombosis does not occur. Ten per cent. of the patients showed a slight general reaction to the first and second injection, which were immediately after the completion of the injection. It does not reappear with further treatment. One patient, who was irregular in attendance, had symptoms suggestive to shock lasting 2—3 minutes, but otherwise there were no ill effects. They found about 40 mg. of elemental iron required to increase the hæmoglobin by 1 per cent. in an anæmic pregnant woman. In comparing the results obtained with iron therapy by mouth, authors feel that response to the treatment with intravenous therapy was more rapid.

J. C. PATEL.

VITAMINS AND ANTI-VITAMINS. Nature, 162, 985-986. December 25, 1948.

An interesting discussion on anti-vitamins in foods arranged by the Nutrition Society took place with Sir Edward Mellanby in the chair. The Chairman can justly be considered the originator of modern concept of anti-vitamins He said that anti-vitamins or toxamin theory is now 20 years old. During this period considerable progress has occurred, in which, even though his original claim that cereals contained anti-vitamin D have not been accepted. Other agents and dietary factors are now clearly recognised as anti-vitamins. L. J. Harris recalled the early work of Eijkmann, the first person to consider anti-vitamin theory in the rice which precipitated polyneuritis. Mellanby worked on rachitogenic properties of cereal products which was the second advance in that line. Sulphonamides due to their bacteriostatic action can be regarded as artificial anti-vitamins. The familiar insecticide Gammexane is anti-vitamin to vitamin inosital. Numerous B vitamins present a very complicated picture. Many B-vitamins are synthesised by the intestinal bacteria, in amount which differ widely in different animals with the result that anti-vitamins may either affect the organisms direct or through the agency of intestinal flora. " There are five different ways in which the action of B-vitamins may be inhibited including (1) failure of intestinal absorption (2) destruction or inactivation of vitamins by toxic substances or bacteria (3) inhibition of bacteria producing the vitamins by antagonists or the absence of essential metabolite. (4) The displacement of the vitamins from the tissues by analogues and (5) exposure of organisms to special stresses, such as infections, pregnancy, and by balance of the major components of the diet."

"Various types of "toxamins" may oppose the action of B-vitamins, but the term 'anti-vitamin' is perhaps best reserved for the structural analogues, which have already been synthesized in relation to aneurin, nicotinic amide, riboflavin, vitamin B_6, pteroyl glutamic acid, pantothenic acid, biotin, choline and inositol. Several natural toxamins have also been reported, including the thiaminase in live yeast which destroys vitamin B_1, a factor in maize which antagonises nicotinic amide, the avidin of raw egg white which inactivates biotin, and the lycomarasmin of wilted tomato plants which antagonizes the bacterial growth-factor, streptogenin."

Plytic acid is an anti-calcifying agent in cereals. It interferes with absorption of calcium which has been shown by McCance in human feeding trials. Absorption of calcium was less efficient with wholemeal bread than with white. Hence, addition of calcium was done to National flour in England. In animals, yeast is given as a source of protein and Bvitamins, but it causes rickets unless vitamin D is given in addition. It is well known that sweet-clover produces hæmorrigic diseases in cattle which can be cured or protected by administration of vitamin K. It has been known that toxic overdosing with one vitamin produces deficiency of other vitamins. This happens in Bvitamins and also fat-soluble vitamnis. Massive overdoses with vitamin A leads in rats, to skeletal fractures and hæmorrages similar to that of scurvy. Similar occurrrence has been recorded in an American child. It is also reported that vitamin A deficiency causes secondary deficiency of vitamin C in rats and silver foxes. Hypervitaminosis A in rats leads to prolonged blood clotting time which can be corrected in time by giving vitamin K. Vitamin E, a powerful antioxident, protects vitamin A from destruction in food stuffs during storage, in the products of their partial digestion passing through the intestinal tract and in the tissues of the consumer. Liability to the effects of vitamin E deficiency is increased by the consumption of readily oxidizable fats, and decreased by adequate dietary supplies and lipotropic factors which facilitate the mobilisation and transference of fat.

J. C. PATEL.

THE USE OF VITAMIN E IN HEART DISEASE. BAER, S. HEINE, W. I. GELFOND, D. B.

The Am. J. Med. Sc. 215 : 542-547, 1948 Tables 4. Ref. 14.

The authors have treated 22 patients of heart disease with Vitamin E 300 to 400 mgm. per day orally for three to four weeks. They did the routine cardialogical investigations but in no case were any detailed investigations done like vital capacity, circulation time, exercise tolerance tests, etc. The routine treatment was continued and Vitamin E was given on top. If patients noted any improvement a placebo was given to exclude psychological factor and in such a case any tendency towards worsening after discontinuation of the drug was also noted.

In eleven patients of congestive cardiac failure there was no definite therapeutic effect in any of them. Only three cases reported slight improvement which cannot be definitely assigned to Vitamin E.

In five patients of angina pectoris one became worse, there was no change in two and in two cases there was questionable improvement as they were no worse after discontinuing the drug.

In six patients of arteriosclerotic heart disease with or without hypertension, none of the cases showed any improvement.

There was no effect on blood pressure E.C.G. and orthodiagrams in all the 22 cases.

There is very little basis for the use of Vitamin E in heart disease. Reports on cardiac derangements produced by deficiency of Vitamin E in animals are conflicting. Even if it did produce cardiac derangements it is very illogical to use it in human heart disease, not due to Vitamin E Deficiency.

S. N. SHAH.

PERIARTERITIS NODOSA. A. W. CONTRATTO, M.D. Arch. of Int. Med. **80** : 567-578, 1947.

The etiology of periarteritis nodosa is not known. The modern trend of the opinion is towards allergy. In many cases a family history of allergy is available and antecedent history of asthma is available. In patients dying shortly after having severe serum or drug reactions lesions of periarteritis nodosa have been demonstrated. They have been produced in animals by sensitising them to foreign proteins. It is very likely to be a manifestation of clinical allergy in which irreversible and distinctive lesions appear in the blood vessels.

Symptomatology of this disease is necessarily vague as it depends upon the organ of which arteries are involved. Abdominal pain not adequately explained by involvement of one organ is most often the presenting symptom. There may be leucocytosis, eosinophilia, persistent high E.S.R., fever, etc. in addition to the symptoms due to the organ involved. The possibility of this disease should be kept in mind in vague cases with prolonged illness and one must be on look-out for nodules under the skin which may be excised and examined. During histological examination of viscera removed at operation its possibility must be kept in mind. Renal involvement is highest in comparison to other organs but this may be due to the fact that it is most fatal and most often diagnosis is made at post mortem. The prognosis is difficult to evaluate. It used to be very grave but report of one case who was diagnosed six years ago and is still alive shows that disease may run a benign course.

The author reports two highly contrasting cases—one case of a Chinese male who had bilateral pulmonary tuberculosis which healed after one year's rest. He had been under the observation of the author for nearly seven years. Every year he had two-three attacks of fever sore throat, swelling of the glands in the neck and pains in the legs. In 1941 he had 2 nodules on the back of forearm which on biopsy and examination established diagnosis of periarteritis nodosa. In 1944 one of the lymph nodes in the neck was excised and showed active tuberculosis. His E.S.R. was twice to thrice normal throughout. He had attacks of headache lasting two to three days and one attack of diplopia. Repeated roentgenograms showed that his pulmonary focus was healed all the time. In the opinion of the author this was a benign case of periarteritis nodosa, involving peripheral arteries only and possibly due to allergy to tubercular proteins. He has good chances of a long life provided he restricts his activities to keep his cervical glands quiescent.

The second case again of a Chinese male whose appendix was removed at the age of 23 (may be due to P.A.N.) he was under observation of the author for about three months. He came for pain resembling nephrolithiasis. Except local tenderness physical, laboratory, and rontgenographic examinations were negative. He developed fever, leucocytosis elevated E.S.R. few red cells and pus cells in the urine and his E.C.G. showed a picture of coronary arterial disease., At this stage there was strong suggestion of periarteritis nodosa in absence of any roentgenographic abnormality of renal, biliary and gastrointestinal tracts. Two nodules appeared near the brachial artery but their examination proved to be inconclusive. He recovered in about 6 weeks. Three months later he was again hospitalised in London for headache and convulsions. He had rigidity of neck and abdomen, loss of ankle jerks, incontinence of urine. B.P. 260-160 urine showed albumin, pus cells and red cells. There was leucocytosis, C.S.F. was normal. Patient developed pain in the renal angle and local oedema. This was explored and a large perinephric hæmatoma and kidneys studded with small infarcts were detected. There was recurrence of bleeding. So the left kidney was excised but patient died the next day of operation. Autopsy confirmed the diagnosis of periarteritis nodosa involving kidneys, mesenteric arteries, coronary and middle cerebral artery.

B. B. YODH.

METABOLIC STUDIES IN DIABETIC ACIDOSIS.—THE EFFECT OF THE EARLY ADMINISTRATION OF DEXTROSE. By MAURICE FRANKS, R. F. BERRIS, N. O. KAPLAN, G. B. MYERS. Arch. Int. Med. V. 80: 739-762, 1947. Tables 12. References *Nil.*

The authors have made a study of 26 cases of diabetic acidosis with coma. The cases were divided in two groups (1) in whom for the first few hours no glucose was given called the saline group and (2) in whom glucose was given from the start called the dextrose group. As soon as the patient was admitted the severity of the disease was computed according to the criteria of Collen. Blood was examined every four hours for sugar, chlorides, carbon dioxide combining power hæmatocrite reading, and plasma specific gravity. Urine was examined every four hours for glucose, acetone, inorganic phosphorus and chlorides. The urine was examined every four hours for acetone bodies. All the patients had fair amount of acidosis. In majority of cases carbon dioxide combining power was below 18 vols. Severity index varied from 3 to 82 average being 35.

In the saline group blood sugar fell to almost normal and remained normal in spite of administration of as much glucose as dextrose group during the later part, and with a relatively small dose of insulin 6.5 units per hour. They were able to retain a greater percentage of sugar and fluids administered. The analysis of chlorides administered, plasma chlorides and urinary chlorides indicated that retained fluids were made available for cells.

In the dextrose group hyperglycæmia was maintained and a large percentage of glucose given was excreted in spite of large dose of 44.5 units of insulin per hour. Most of the administered fluids were excreted with glucose and whatever was retained was retained as hypertonic saline indicating that it was retained in the interstitial spaces and cellular dehydration remained the same or was made worst. Two cases with a low severity index had a stormy course and went into shock and circulatory failure.

The time required for disappearance of acetone in urine and rise in carbon dioxide combining power was approximately the same in both the groups.

The mortality in saline group with average severity index 40 was 36 per cent in the dextrose group with average severity index 37 was 52 per cent.

It is customary to administer glucose with large doses of insulin in cases of diabetic coma so as to overcome acidosis. In animal experiments it has been shown that hyperglycæmia helps the oxidation of glucose and glycogenation of liver even in absence of insulin. The author has shown that if insulin is given it is more useful at normal sugar level and glucose metabolism is much more efficient near normal limits. The time required to abolish acidosis is the same. Hyperglycæmia is burden on the heart and blood vessels and patient is likely to develop shock and circulatory failure. At high sugar level kidney cannot reabsorb glucose and fluids, polyuria is maintained and dehydration cannot be relieved.

S. N. SHAH.

SURGERY

TUBERCULOSIS OF THE CERVICAL LYMPH NODES. THE PRESENT SURGICAL STATUS. CHARLES W. LESTER. Surg. Gynæc. Obstet. 87 : 719-724, Dec. 1948.

In the United States tuberculosis of the cervical lymph nodes is fast becoming a rare disease. The reason is that tuberculosis in dairy cattle has almost been eliminated, widespread removal of septic tonsils removes the portal of entry, and there is a marked decrease in the chances of exposure to tuberculosis. " In 1915 a positive tuberculin test in a child over 2 years of age was not considered of great significance ; but in 1948 a positive tuberculin test at any time in childhood has considerable diagnostic weight " (in the U.S.A.).

A firm swelling in the neck in children or young adults usually starting beneath the angle of the jaw which is tender at first but later painless and tends to extend rather than subside is probably tuberculosis. An acute infection in the same location subsides or suppurates in less than a month. The lymphomas feel more elastic and, while they may present a massive swelling, give the impression of being more discrete. The congenital cystic structures are stationary and have typical locations.

If the tuberculous nodes are merely local manifestations of an active systemic disease no surgical intervention is indicated. So also in the exudative phase of the disease, *i.e.*, while the nodes are tender and the patient toxic, bed rest and all the supportive treatment applied to pulmonary tuberculosis are indicated.

Roentgen therapy chiefly acts by producing fibrosis around the infection, and is therefore of value early before caseation necrosis has developed and late, when cold abscesses drain through chronic sinuses.

Streptomycin is of value but should be used judiciously because when the drug has been given for sometime the organisms in the lesion are found to be streptomycin-resistant. This antibiotic is most effective in the acute exudative phase of tuberculosis and of scant value in the caseous and fibrotic phases. It should however be used as a prophylactic measure with surgery to prevent the spread or activation of the disease elsewhere. The dosage recommended is 10 mg. per pound of body weight, maximum of 1 gram in 4 divided doses per day. It is started a day before the operation and not discontinued before two weeks after the operation.

Two important nerves must be saved in the dissection of cervical nodes. The marginal mandibular branch of the facial nerve crosses the angle of the mandible and lies just caudad to it as far as the facial vessels where it ascends onto the face. It lies beneath the platysma and on the deep cervical fascia. An incision a finger's breadth beneath the mandible will avoid it, and if it is necessary to dissect upwards the dissection must hug the capsule of the node. The eleventh nerve crosses the transverse process of the atlas under the posterior belly of the digastric and enters the upper third of the st. mastoid to emerge about the middle of the posterior border to supply the trapezius.

Many practical hints are given in this article for the performance of the operation for removal of tuberculous lymph nodes in the neck.

E. J. BORGES.

THROMBO-ANGEITIS OBLITERANS.—RESULTS OF SYMPATHECTOMY AND PROGNOSIS. By J. B. KINMONTH. The Lancet, 2: 717-720, 1945 Figures 4. Charts 3. References *Nil.*

Cases appearing in the literature in last 14 years have been reviewed. The diagnosis of the disease is fairly easy from characteristic history, evidence of ischæmia, loss of arterial pulse and often presence of superficial phlebitis. Occasionally oscillometry and arteriography have to be employed. Among etiological factors number of Jews was not great and W. R. was positive in only one case. Two patients completely gave up smoking but without any benefit.

The natural course of disease was episodes of activity separated by months or years of quiescence longest of which was 14 years.

Clinically the disease can be divided into three types :—(1) Obstruction of a main vessel. Popliteal pulse is obliterated. Claudication with pronounced postural colour changes are main symptoms. Gangrene and ulceration are rare. (2) Obstruction of small vessels :—Popliteal pulse remains palpable but pulse at ankle diminished or lost. Pain in the foot, constant erythrocyanosis, coldness, ulceration and gangrene of toes often occurs. (3) Mixed type where both types of vessels are affected and symptoms of both are present.

Reports on results of sympathectomy are infrequent and statements on effects on claudication are vague. But results in relief from claudication were obtained in cases where smaller vessels were involved. Chances of survival of the limb were better in disease of small vessels than in the other two types.

It is impossible to say how far sympathectomy was able to stop or slow the progress of the disease. Prophylactic sympathectomy did not give complete protection.

Among fatal cases thromboembolic phenomenon predominated.

S N. SHAH.

DOSAGE OF PALUDRINE

Dr. J. M. Mungavin, Medical Service Department, I.C.I. (India) Ltd., writes that in view of the changes in the dosage of Paludrine that was announced in last July, two new sizes 0.3 Gm. for adults and 0.025 Gm. for young children are now available.

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Examples: 1. Coller, F. A., and Maddock, W. G.: The Function of Peripheral Vasoconstriction, Ann. Surg. **100**: 983-992, 1934.

2. White, J. C., and Smithwick, R. H.: The Autonomic Nervous System, pp. 271, New York, the Macmillan Company, 1941.

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SYNTHETIC FOLIC ACID IN TROPICAL MACROCYTIC ANÆMIA

J. C. Patel* and Y. M. Bhende†

Darby *et al.* [3] (1945) used folic acid successfully in the treatment of sprue. Das Gupta and Chatterjee[4] (1946) reported its success in 8 cases of nutritional macrocytic anæmia in India. Spies[5] (1947) and Spies *et al.*[6] (1948) reported that folic acid produced a satisfactory clinical and hœmopoietic response in each of 32 cases of nutritional macrocytic anæmia in relapse. Benjamin-Allen[1] (1948) treated 6 cases of macrocytic anæmia associated with pregnancy by folic acid with marked benefit. The following is a report of 6 cases of tropical macrocytic anæmia treated with folic acid.

MATERIAL AND METHODS

The cases were admitted to the P. G. Singhanee Hindu Hospital, Bombay, and were studied by the method described by us[2]. All had macrocytic anæmia with an initial red cell count of less than 3.0 million per c.mm. The marrow showed the presence of megaloblasts in all cases. The blood count was repeated every 7 days, and in some cases more often. These were 4 males and 2 females and the ages ranged from 20 to 50 years.

CASE NO. 1

A female, aged 30, was admitted for general weakness, loss of appetite, frequency of stools, occasional vomiting and frequent attacks of stomatitis. She had delivered a month before. The symptoms had started about 4 months before the delivery and had gradually become aggravated. In spite of these symptoms she was nursing her baby. Her economic status was poor. She was a vegetarian. On examination she was pale and emaciated. The tongue was pale and smooth. The liver and the spleen were not palpable. A hæmic murmur could be heard in the precordial region. Examination of the respiratory and the central nervous systems showed nothing abnormal. Urinalysis and examination of the fæces were negative. Gastric analysis showed presence of free acid. The Wassermann reaction of the blood was negative. Fluoroscopy of the chest showed nothing abnormal. Her blood count on admission was as follows :— R. B. C. 1.90 mill. per c.mm., Hb. 6.05 gm., M. C. V. 112.2 c. u., M. C. H. C. 27.7 per cent., S. I. 0.79 The marrowgram showed a megalo-normoblastic reaction. She was treated with 20 mg. of folic acid, daily, for 14 days. At the end of 14 days examination of the blood gave the following figures :—R. B. C. 3. 0 mil. per c. mm., Hb. 9.7 g.m., M. C. V. 103.3 c. u., M. C. H. C. 30.6 per cent., S. I. 0.87.

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COMMENT

She made a good recovery; the appetite had improved and her weight increased by 2 pounds. She was discharged against medical advice as she wanted to go home and nurse her baby. The response in this case to the folic acid treatment was an optimum one. The marrowgram before and after treatment was as follows :—

	Before treatment.	8 days after treatment.
	Per cent of Nucleated cells.	
N. Seg.	10.0	13.0
N. Stab, ...	14.0	15.0
N. Juveniles	3.2	5.3
Myelocytes	6.0	4.0
Premyelocytes	2.0	0.5
Myeloblast	0.0	0.0
Eosinophils	2.0	1.1
Basophils	0.0	0.0
Monocytes	0.0	0.0
Lymphocytes	7.5	4.5
Megaloblasts :		
Hæmoglobinised	3.0	0.5
Non-Hæmoglobinsed ..	8.5	2.2
Pro-erythroblasts	6.0	0.2
Normoblasts :		
Type 1	18.5	3.6
„ 2	5.2	33.3
„ 3	14.1	17.8

CASE NO. 2

A male, aged 50, was admitted for frequency of stools (10-15 per day) and griping pain on the right and left sides of the abdomen for 2 months. There was cough, breathlessness on exertion and general weakness for the last 15 days, and, œdema over the face and the feet for the last 20 days. On examination he was found to have œdema on the legs as well. His liver was enlarged 3 fingers below the costal margin. The spleen was not palpable. Examination of the central nervous system did not reveal any abnormality. Examination of the respiratory system showed a barrel-shaped chest with hyperresonant note and dry foreign sounds. He had occasional extra-systoles. The blood pressure was 120-60. Examination of the urine showed nothing abnormal. Examination of the fæces showed a large number of leucocytes and fatty acid crystals. The Wassermann reaction of the blood was negative. There was a histamine-fast achlorhydria. His sputum was negative for M. tuberculosis. The blood urea was 40 mg. per 100 ml. He was a petty clerk and had to put in long hours of work. He was a vegetarian and unmarried. His diet was irregular and deficient in nutritional elements, particularly so during the last two months when he was ill. His blood count on admission (14-1-47) was as follows :—R. B. C. 1.92 mill. per c.mm., Hb., 10.03 gm M. C. V. 169.1 c. u., M. C. H. C. 30.8 per cent., S. I. 0.89. The Van den Bergh reaction was negative. The marrowgram showed a megalo-normoblastic reaction. He was given 30 mg. of folic acid by mouth on 1st day and 20 mg. for next 27 days. Eighteen days after the beginning of folic acid therapy his blood count was :—R. B. C. 3.04 mill. per c.mm., Hb. 11.41 gm, M. C. V. 120.6 c.u., M. C. H. C. 30.0 per cent., S. I. 0.86 and on 18-2-47 (28 days) it was :—R. B. C. 3.02 mill. per c.mm., Hb. 11.24 gm., M. C. V. 112.2 c.u., M. C. H. C. 30.0. per cent., S. I. 0.87.

COMMENT

His general condition had improved considerably. The œdema had disappeared and the appetite improved. There was an optimum improvement in first 18 days but it was not maintained in spite of continued administration of folic acid.

CASE NO. 3

A female, aged 35, was admitted for general weakness, flatulence, pain in the abdomen and poor appetite for 1 year, swelling of the face and feet for 1½ years and palpitation and giddiness for 6 months. She gave a history of having suffered from dysentery for 1 month, 1½ years ago. She had had her menopause 2 years ago. On examination she was pale and there was an icteric tinge. She had œdema of the face and feet and spoon-shaped nails. A hæmic murmur was heard over the precordial region; the lungs were normal. The liver and the spleen were not palpable. Examination of the central nervous system did not reveal any abnormality. She was a housewife, a vegetarian, and her economic status was poor. Examination of the urine showed nothing abnormal. Examination of the æces showed few leucocytes with Charcot Leyden crystals. The Wassermann reaction of the blood was negative. Gastric analysis showed the presence of free acid. On admission (17-1-47) her blood count was as follows :—R. B. C. 2.60 mill. per. c.mm., Hb. 8.65 gm. per 100 c.c., M. C. V. 128.8 c.p., M. C. H. C. 25.8 per cent., S. I. 0.73. The Van den Bergh reaction was negative. The marrowgram showed a megalo-normoblastic reaction. She was given by mouth 40 mg. of folic acid on the 1st day followed by 30 mg. a day for the next 13 days. On 31-1-47 her blood count was :—R. B. C. 2.60

mill. per c.mm., Hb. 8.30 gm., M. C. V. 111.5 c.p., M. C. H. C. 28.6 per cent., S. I. 0.80. As there was no improvement with folic acid it was stopped and instead she was given 15 grains of Blaud's pills three times a day from 1-2-47 to 10-2-47. She improved as shown by the following figures :—R. B. C. 3.20 mill. per c.mm., Hb. 8.99 gm., M. C. V. 100.0 c. u., M. C. H. C. 28.0 per cent., S. I. 0.77.

COMMENT

Even though she had a macrocytic, hypochromic anæmia, with a megaloblastic marrow, she failed to respond to folic acid therapy. Subsequent administration of iron produced good hæmopoietic response.

CASE NO. 4

A male, aged 20, was admitted for general weakness and loss of appetite. Eight months before he had fever for 3 days, after which his illness began with loss of appetite. There was no frequency of stools. He complained of fullness in the abdomen particularly after food, flatulence, nausea and vomiting. In the course of 8 months he had lost 45 lbs. in weight. He had had repeated attacks of glossitis. He felt so weak during the last 15 days of his illness that he was confined to bed. He was a student, a vegetarian, and had not suffered from any other illness. Examination showed marked emaciation (weight 73½ lbs.) a dry skin with follicles and a yellowish tinge in the sclera. There was pavement like appearance on the skin of the shins. The tongue was red, smooth and inflamed. The liver and the spleen were not palpable. Examination of the heart showed a hæmic murmur. The lungs and the central nervous system were normal. Urine analysis and examination of the fæces did not show any abnormality. The Wassermann reaction of the blood was negative. Gastric analysis showed presence of free acid. The marrow showed megaloblastic reaction. On admission his blood count was :— R. B. C. 1.56 mill. per c.mm., Hb. 6.78 gm. per 100 c.c., M. C. V. 176.2c.u., M. C. H. C. 28.2 per cent., He was given 20 mg. of folic acid by mouth for weeks. His blood count on the 14th day (18-4-47) was :—R. B. C. 2.40 mill. per c.mm., Hb. 11.20 gm., M. C. V. 154.1 c.u., M. C. H. C. 30.2 per cent., S. I. 0.86.

On 11-5-47, five weeks after the beginning of therapy his blood count was :— R. B. C. 3.440 mill. per c.mm., Hb. 10.8 gm., M. C. V. 105.8. c.u., M. C. H. C. 30.0 per cent., S. I. 0.85.

It was found that even thoughty here was an increase by two million in his red cells there was no proportionate increase in the hæmoglobin. He was given iron tablets (Blaud's Mass grs. xv Tid.) on 11-5-47, and his blood count 6 weeks later was :—R. B. C., 4.28 mill. per c.mm. Hb. 13.8 gm., M. C. V. 82.9 c.u., M. C. H. C. 36.1 per cent., S. I. 1.12. His weight increased by 24-lbs. during his 5 weeks' stay in this hospital. (He volunteered information, 3 days after therapy that he felt well and his appetite had improved considerably.)

COMMENT

This patient was one of the series, who was benefitted considerably by folic acid therapy and showed dramatic improvement as regards his appetite, weight, glossitis and blood.

CASE NO. 5

A male, aged 24, was admitted for purulent discharge from urethra, balanitis and conjunctivitis of 10 days duration and fever for 4 days. He also complained of general weakness for the last 3 months and flatulence with occasional attacks of looseness of the bowels and vomiting for the last 2 months. He had suffered from jaundice 8 months previously. On examination his skin was found to be pale and had a yellow tinge. His tongue was smooth and pale. He had œdema of the legs, and hæmic murmur was audible over the precordial region. Examination of the respiratory and the central nervous systems showed no abnormality. The liver was not palpable; the spleen was enlarged 1 finger below the costal margin. Examination of the discharge from the urethra showed presence of N. gonorrhœae. Examination of the fæces was negative. The Wassermann reaction of the blood was not done. Gastric analysis showed presence of free acid. He was a vegetarian, of poor economic status. and was unemployed for the last 4 months. He was treated with penicillin in the usual dosage for his urethritis which cleared up completely in 10 days. The temperature subsided and remained normal after the first 5 days. On institution of treatment (11-5-47) his blood count was:—R. B. C. 1.76 mill. per c.mm., Hb. 6.05 gms.,M. C. V. 107.9 c.u., M. C. H. C. 31.8 per cent., S. I. 0.9. The Van den Bergh reaction was indirect positive and his icteric index was 15 units. The marrowgram showed a megalonormoblastic reaction. He was given 20 mg. of folic acid a day by mouth for 19 days. His blood count on the 7th day (18-5-47) was:—R. B. C. 2.08 mill. per c.mm., Hb. 8.3 gm., M. C. V. 139.4 c.u., M. C. H. C. 28.6 per cent., S. I. 0.81. On the 14th day (25-5-47) examination of the blood gave the following figure:—R. B. C. 3.24 mill. per c.mm., Hb. 10.03 gm., M. C. V. 108.0 c.u., M. C. H. C., 28.6 per cent., S. I. 0.87. On the 37th day (18-6-47) the blood count was:—R. B. C. 3.68 mill. per c.m., Hb. 12.9 gm., M. C. V. 114.1 c.u., M. C. H. C. 30.7 per cent., S. I. 0.88. His weight had increased by 12 lbs.

COMMENT

This patient responded well to folic acid therapy.

CASE NO. 6

A male, aged 23, was admitted for general weakness of 6 months duration which had increased considerably during the last 1 month. He had, in addition, pain in the abdomen, flatulence, sore tongue and looseness of the bowels 3 to 4 watery stools per day during that time. There was no vomiting. On examination, he was found to be pale. There was no swelling of the feet. Examination of the lungs, the central nervous system and the alimentary system showed nothing abnormal. The hæmic murmur was audible over the precordial region. But the urine and the fæces examination did not show any abnormality. Fluoroscopy of the chest did not reveal any lesion. The Wassermann reaction of the blood was negative. Free acid was found on gastric analysis. The marrowgram showed a megalo-normoblastic reaction. He was a vegetarian and was working as a shop assistant. He was unable to take adequate diet due to digestive disturbances he had during the last 6 months. On admission (15-5-47) his blood count was:—R. B. C. 2.60 mill. per c.mm., Hb. 10.38 gm., M. C. V. 123.07 c.u., M. C. H. C. 32.4 per cent., S. I. 0.92. He was given orally

20 gms. of folic acid daily for 29 days. On 29-5-47, 14 days later, the examination of the blood showed :— R. B. C. 2.92 mill. per c.mm., Hb. 12.4 gm., M. C. V. 136.9 c.u., M. C. H. C. 31.0 per cent,, S. I. 0.88. On. 12.-6-47, 4 weeks later, the blood count was :—R. B. C. 3.80 mill. per c.mm., Hb. 14.38 gm., M. C. V. 107.8 c.u., M. C. H. C. 35.0 per cent., S. I. 1.0.

His weight increased by 10 lbs. during the treatment. Even though improvement was below the optimum during the first 14 days, there was a delayed but adequate response subsequently.

COMMENT

There was optimum improvement in 4 cases (Nos. 1, 2, 4 and 5) within the 1st fortnight, delayed response (in a period of 28 days) in 1 case (No. 6) and no improvement in 1 case (No. 3). In 1 case the (No. 2) optimum improvement in the first 14 days was not maintained in the next fortnight in spite of continued administration of folic acid. In case No. 6, there was delayed but adequate response. Case No. 3 failed to respond to folic acid during the 1st fortnight. When folic acid was discontinued and iron given instead, during the next 14 days, she responded well. The possibility of a delayed response to folic acid cannot be excluded, but this was the only case which did not show any response during the 1st fortnight's therapy with folic acid. The most dramatic response occurred in case No. 4 where the patient developed a voracious appetite in 4 days and there was an increase in weight of 24 lbs. in 5 weeks. Nausea disappeared on the 2nd day and stomatitis began to improve on the 4th day. There was a rapid improvement both in the red blood cells and the hæmoglobin upto a stage (upto 28th day). Increase in the erythrocytes was very little in next 10 days and there was no further improvement in hæmoglobin. In the following 7 days not only was there no improvement in the number of red blood cells and the Hb but the gained level was not maintained. With the administration of iron for a period of 1 month, there was improvement both in the red blood cells and the Hb. The number of cases reported is too small to draw any inferences, but it may be said that in the majority of cases of tropical macrocytic anæmia, folic acid proved to be effective.

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TABLE I.

Case No.	Age Sex.	Examination of Blood Before Treatment					Marrow-gram	Van den Bergh re-action	Folic acid in mg. per day and number of days of treatment	After Treatment					Days	Remarks.
		RBC in mill. per c. mm.	Hb. in gms. per cent.	MCV c. μ	MCHC per cent	S.I.				RBC	Hb.	MCV	MCHC	SI		
1	20/F	1.90	6.05	112.2	27.7	0.79	Megalo-normo-blastic	–ve	20 mg. for 14 days.	3.0	9.7	103.3	30.6	0.87	14	Optimum improvement.
2	50/M	1.92	10.03	163.0	30.8	0.89	Megalo-normo-blastic	–ve	30 mg. 1st day. 20 mg. x 13 days. 20 mg. x 14 days. 28 days.	3.0 3.32	11.41 11.24	120.6 112.2	30.0 30.0	0.81 0.87	14 28	Optimum in 1st 14 days No further improvement.
3	35/F	2.60	8.65	128.8	25.8	0.73	Megalo-normo-blastic.	–ve	40 mg. 1st day. 30 mg. 13 days, Blands pills gr. XV T.I.D. x 10 days.	2.60 3.20	8.30 8.99	111.5 100.0	28.6 28.0	0.80 0.77	14 24	No response to FA treatment but responded to iron subsequently.

TABLE I.—(*Contd.*)

Case No.	Age Sex	Examination of Blood Before Treatment					Marrow gram.	Van den Bergh re-action	Folic acid in mg. per day and number of days of treatment	After Treatment					Days	Remarks.
		RBC in mill. per c. mm.	Hb. in gms. per cent.	MCV c. μ	MCHC per cent.	SI				RBC	Hb.	MCV	MCHC	SI		
4	20/M	1.56	6.78	176.2	28.2	0.80	Megalo-blastic	–ve	20 mg. x 35 days	2.40	11.20	154.1	30.2	0.86	14	Optimum improvement for 28 days. No further improvement till iron was given.
										3.32	10.50	108.0	29.1	0.83	28	
									Iron tablets for 1 month from 45th day to 70th day.	3.40	10.80	105.8	30.0	0.8	39	
										3.20	10.67	..	...	..	45	
										4.28	13.80	82.9	36.1	1.12	87	
5	24/M	1.76	6.05	107.9	31.8	0.9	Megalo-blastic.	–ve	20 mg. x 19 days.	3.24	10.03	108.0	28.6	0.87	14	Optimum improvement.
										3.68	12.9	114.1	30.7	0.88	37	
6	23/M	2.60	10.38	123.8	32.43	0.92	Megalo-blastic	–ve	20 mg. x 29 days.	2.92	12.4	136.9	31.0	0.88	14	Delayed response.
										3.80	14.38	107.8	35.0	1.0	29	

URINARY SCHISTOSOMIASIS IN INDIA

WITH A REPORT OF ONE CASE

A. E. deSa and L. Monteiro *

Human Schistosomiasis is a disease produced by three species of Schistosomes; *S. hæmatobium*, *S. mansoni* and *S. japonicum*. Each of these species has a well marked geographical distribution, and in affected areas, the parasites produce serious ravages. In India, infections contracted in endemic areas have been reported. In addition, nine authentic autochtonous cases of urinary schistosomiasis have also been described. The first case was reported by Powell[13] (1903) in a resident of Bombay who had painless hæmaturia and no constitutional symptoms. The second was recorded by Sewell[14] (1904) in a British soldier who had lived for four years in India and had never been to Egypt or Africa. The third was reported by Christophers and Stephens [6] (1905) in a resident of Madras, and two by Wardrop[16] (1906) in two British soldiers who contracted the disease in India and who had never lived in an endemic area. Hooton[11] (1914) recorded another case in a Parsi girl at Rajkot, and Harkness[10] (1922) in a British soldier. Mello[8] (1936) quotes one definite case in a child 9 years old, who resided in a village in Goa which had been inhabited by African troops infected with this trematode. Ova of *Schistosoma hæmatobium* were present in the urine and fæces. Recently Andreasen and Suri[3] (1945) recorded a case in a Sikh sepoy who had not been out of India. He was stationed for a short time at Poona where West African troops were posted. A total of nine cases therefore, all of them produced by *Schistosoma hæmatobium* have been reported to date. Autochtonous infections by the other two human schistosomes have not been recorded in India. The occurence of these isolated cases indicates that some molluscs in this country are capable of harbouring the larval stages of *S. hæmatobium*. The importance of this fact cannot be over-emphasized; especially in times of war when large numbers of men coming from Africa, China or Japan, or Indian troops returning from these endemic areas might introduce the infection into India. That older workers were alive to this danger is seen by the reports published in the wake of the first world conflagration. Sewell[15] in 1919 opined that since the common molluscan hosts of the human schistosomes were not found in India, the possibility of endemic schistosomiasis was remote. Kemp and Gravely[12] (1919) attempted to infect experimentally the various molluscs found near Secunderabad with the miracidia of *S. hæmatobium.* All these molluscs proved refractory to infection. Mello[8] (1936) working along similar lines in Goa reported that in the species *Limnæ luteola var. pinguis Dorhn,* miracidial attraction was very active and was often followed by penetration. There were no sporocysts or cercariæ found in this mollusc four months later. He also detected a case of natural infection of Melanoides tuberculatum with furcocercous cercariae indistinguishable from that of *S. hæmatobium.* He concluded that sporadic cases of Schistosomiasis occuring in India may have been due to a fortuitous infection of some molluscan hosts which are not normally infected in nature. Recently, this problem was studied again by Mukerji, Bhaduri and Narayan (1944) who carried out an examination of the fæces and urine of 22,317 West African troops stationed in the Ranchi area, and found that 2,061 men were passing ova of *S. hæmatobium* and 38, of *S. mansoni.* Experimental infection of various molluscs collected in the Ranchi and Calcutta areas with miracidia of *S. hæmatobium* and *S. mansoni* yielded negative results. The molluscan intermediate hosts of human Schistosomes belong to the genera Bulinus and Physopsis. These species are not found in India. In a personal communication S. R. Rao, Parasitologist to the Government of Bombay, who carried out a survey of snails in the Province of Bombay, states that these molluscan hosts are not found in the Province. Bhalerao[5] (1948) in reviewing blood fluke infections in India says: 'The clinical, epidemiological and experimental data, obtained so far, do not warrant the conclusion that urinary bilharziasis may become endemic in India. Animal Schistosomiasis on the other hand, is a fairly widespread disease causing considerable damage to the livestock in this country. Six distinct species have been recorded in India; *S. spindalis, S. nasalis, S. indicum, S. incognitum, Ornithobilharzia bomfordi and Ornithobilharzia nairi.* It is reported, that, on rare occasions, animal schistosomes may infect man. *S. bovis, S. inter-calatum* (which are not found in India), and *S. spindalis* may occasionally be responsible for infection in man. Though *S. spindalis* is common in India, no human case has so far been reported. Moreover, there is no authentic case where urinary schistosomiasis has been produced by a parasite of animal origin. These animal schistosomes, however, may be responsible for cercarial dermatitis or Swimmer's itch, several cases of which were published by Cort[7] (1928) from Mysore.

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Recently, we have come across one definite autochtonous case of hæmaturia due to *S. haematobium.*

CASE REPORT

A Hindu female, aged 19 years, was admitted to the hospital with a history of painless hæmaturia of 9 years duration. The patient is a native of Guhagar Taluka, Ratnagiri District and has never been out of India. Besides her village, the only other place she has resided in is Bombay. On being questioned about the incidence of hæmaturia in her village, she mentioned that her brother had also suffered from the same complaint some years ago. He also had never left the shores of India.

On examination the patient did not seem to be troubled by the hæmaturia. There were no constitutional symptoms. The liver and spleen were not enlarged. The rectum and the genital tract were normal. The urine before treatment with antimony tartrate showed a large number of eggs of *S. hæmatobium*, in addition to red blood cells, epithelial cells, pus cells and calcium oxalate crystals. After treatment degenerated eggs continued to be passed in the urine and evidence of cystitis persisted. The stools showed hookworm and whipworm ova, and cysts of *entamœba histolytica*. Ova of Schistosomes could not be detected.

DISCUSSION

Two interesting features of this case are the fact that the patient has never left the shores of India, and the early onset of the hæmaturia. A large number of people in her village were apparently affected with identical symptoms and the patient asserted with confidence that the hæmaturia tended in every instance to diminish and disappear about the age of puberty.

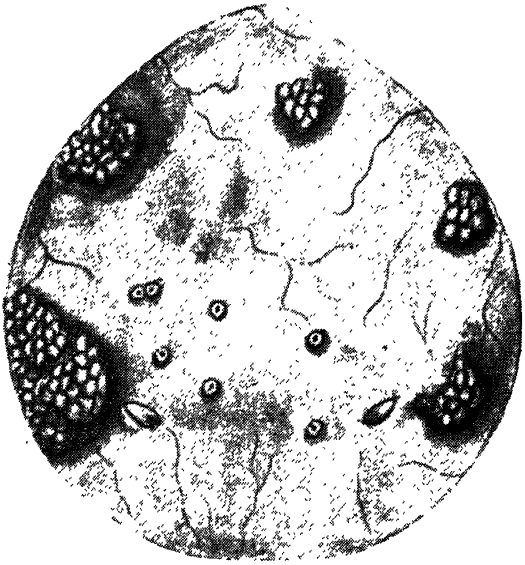
The fact that so many of her immediate circle of friends suffered from similar symptoms suggested a common causative factor.

It is the experience of one of us (A.E.deS.) that villous papilloma of the bladder is a rare neoplasm in Indians. Of the three that he has encountered in India in the last 11½ years only one occurred in an Indian; the other two cases occurred in a European and an Anglo-Indian patient respectively.

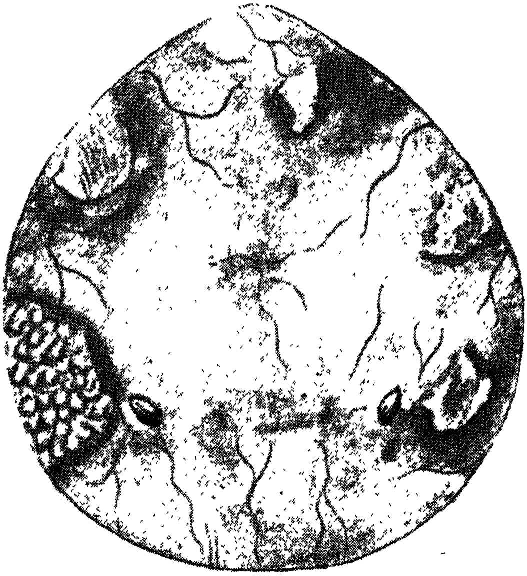
Though a large number of cases have been described in the aniline dye workers in Friedrichshafen, there was no such obvious occupational cause in this small Ratnagiri village. For this reason, as well as because the vesical papillomata did not conform to the usual neoplastic pattern, as will be later indicated, a search for Bilharzia ova in the urine was instituted.

The cystoscopic findings are recorded schematically on the accompanying chart. The papillomata did not have the delicate waving fronds of the true neoplasm. On the contrary the processes on the papillomata were coarse and stunted and had a curiously granular greyish-yellow appearance.

The cystoscopic appearance did not suggest a malignant transformation in benign papillomata.



Cystoscopic appearance before commencement of treatment.



Cystoscopic appearance at completion of treatment with antimony.

The history of spontaneous cessation of symptoms in the majority of her co-villagers raises the important question of whether the disease is self-limited and tends ultimately to burn itself out. In this connection the case history and cystoscopic findings in the patient's brother who was sent for so that a complete urological examination could be undertaken on him, are illuminating. His case is reported at the end of the paper.

The radiological findings in this case—both the plain radiogram of the urinary system, as well as the descending pyelogram were non-contributory.

Afifi (quoted by Lowsley 1944) has drawn attention to the 'cloud-like' shadows and clear demarcation of the bladder and lower ureter in long standing bilharziasis of the bladder, caused by calcification in their walls. These calcifications, produced by infiltration of the urinary tract with calcified ova, may attain the density of osseous tissue.

TREATMENT

Though many variations in the mode of the administration of the drug have been suggested, the treatment of Schistosomiasis still revolves round the antimonials. Since 1918, when Christophersen standardised the treatment with intra-venous administration of tartar emetic, an over-all dose of 20-30 grains depending upon the weight of the patient has been considered adequate to cure. The injection is initiated with half a grain intravenously and is increased by half a grain every alternate day, till a maximum of 2½ grains is reached.

An organic compound of antimony, Fouadin, has found favour with some clinicians.

More recently, Alves and Blair[1] (1946) (as quoted by Girjis and Aziz[9] 1948) have developed a more intensive treatment with antimony tartrate, administering the total estimated dose of the drug in two to six days. The total dose is estimated by allowing 1 grain of the drug for every 5 kgm. of the patient's body-weight. The intravenous injection should, according to Alves and Blair occupy a period of 5 minutes, "the slow and steady injection of the drug is of fundamental importance in the success of the treatment."

Undesirable side reactions are more likely to result from this form of treatment. These include vomiting, cough, tightness of the chest, pain in the back and joints and electrocardiographic evidence of myocardial damage.

SURGICAL TREATMENT

Following established principles, complications are handled as they arise and resistant papillomata and ulcers may need fulguration.

Repeated cystoscopy is essential to estimate the efficacy of treatment and for the early detection and treatment of a not uncommon complication, carcinoma.

The patient whose case is here reported has received so far a total dose of 12 grains of antimony tartrate given in 1 gr. doses every third day. There has been a striking diminution in the hæmaturia clinically, though degenerated ova of the schistosoma and microscopic evidence of hæmaturia were still present 21 days after commencing treatment.

Cystoscopic examination repeated six weeks later showed a great decrease in the papillary growths in the bladder. Most of these were replaced by yellowish white sandy patches on the bladder wall. There still remained, however, one large papilloma above the right ureteric orifice which might need subsequent fulguration.

CRITERIA OF CURE

Christophersen (1918-1919) believed that antimony killed not only the adult worm but also the embryo deposited in the terminal vessels. The only criterion of true relapse was therefore according to him, the presence of living ova in the urine. Girgis and Aziz[1] (1948) however consider that even the presence of dead ova in the urine is an indication of failure to cure, because they may indicate the presence of a live worm in the bladder mucosa or its neighbourhood.

COMPLICATIONS

Carcinoma ranks as the commonest and most serious complication of the disease. Early and thorough treatment and repeated cystoscopy in order to detect malignant transformation at its earliest stages are valuable measures in controlling the disease.

The case of this patient's brother brings out a rare complication of urinary bilharziasis, hydronephrosis.

In order to pursue the question of the prevalence of the disease in the patient's district and family, the patient's brother was sent for, for the purpose of clinical, laboratory and cystoscopic examinations.

He was a boy of 18 years who gave a history of hæmaturia from early childhood upto the age of 12 years. The hæmaturia had not been excessive at any time and had gradually ceased. There were no positive clinical findings and a painstaking examination of the urine did not reveal the ova of the parasite. Cystoscopy revealed marked cicatrisation and trabeculation around the right ureteric orifice. There was a small button like elevation above and internal to the right ureteric orifice which was covered with what appeared to be white phosphatic deposit. The whole appearance of the bladder wall in the region of the right ureteric orifice was suggestive of an infective process that had healed and scarred over. A plain X-ray of the urinary tract was non-contributory. A descending pyelogram revealed a moderate degree of hydronephrosis and hydroureter on the right side, the hydroureter extending right down to the bladder wall. The findings on descending pyelography dovetailed into the cystoscopic appearances, and it was concluded that fibrosis of the bladder wall in the region of the intramural segment of the ureter had caused compression of its terminal part.

The intramural segment of the ureter was therefore dilated under spinal anæsthesia with a ureteric probang and a ureteric catheter was passed beyond the site of the obstruction into the ureter.

The patient has been requested to return after a month for a repetition of descending pyelography. One will then be able to estimate the degree of improvement that has resulted from the ureteric dilatation.

CONCLUSION

The possibility of a small endemic focus of schistosomiasis cannot be absolutely ruled out unless a survey of the population in the village concerned is carried out. A more detailed study of molluscan hosts in relation to schistosomal infection may also be useful.

SUMMARY

1. One autochtonous case of urinary bilharziasis is reported.
2. The possibility of an endemic focus is discussed.
3. The incidence of the disease in India is briefly reviewed.
4. The complications and treatment are considered.

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MEDICAL PROGRESS

PROGRESS IN THERAPEUTICS, 1949

V. Iswariah *

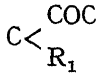
(*Continued from page 338*)

IX. ADVANCES IN 'SYSTEMIC THERAPY.'

NERVOUS SYSTEM

ANALGESICS

Pethidine or dolantoin or demerol, now official in the 1948 British Pharmacopeia, is rapidly becoming a habit forming drug. Symptoms of addiction resemble those of cocaine and atropine. It is no wonder therefore that newer analgesics are making their appearance claiming to be improved substitutes for the older ones. The side actions of morphine, the queen of analgesics seems to have been the drive at an earlier stage for improved ones. Attempts at 'reforming' morphine by suitable structural changes as in diamorphin (heroin) dicodid, dihydromorphinone, etc., have not yielded satisfactory results. Metapon hydrochloride which is a derivative of morphine has less tendency for emesis, respiratory depression, intolerance, etc. It is administered in 6-9 mg. doses in capsules.

A group of analgesics with chemical structure  $C<^{COC_2H_5}_{R_1}$ called methadon, miadone, adanon or A. N. 148 started their career claiming to be improved pethidine products. Amidone or physeptone is 6 dimethyl amino 4.4 diphenyl heptanone hydrochloride. It has been found to be very effective in giving relief in pain in ischæmia following occlusive arterial diseases. Prior to amidone relief to this kind of pain could only be had with drastic measures like nerve crushing, nerve section, alcohol injection into the nerve sheath, etc. Amidone (first prepared in Germany) in 5-15 mg. doses in capsules or tablets gave relief to pain in 20-30 minutes. The effect lasted from 12-30 hours. No cumulative effect has so far been noticed as patients have been taking daily for 30-60 days which amounts to an aggregate dose of 2,400 mg. No side effects like change in heart rate, blood pressure, respiration, temperature, etc., have been noticed. The relief to pain was obviously by cortical depresent action and not by relieving ischemia. It is also of value in Raynaud's disease, nocturnal cramps, arterioscleros is obliterans, thromboangitis obliterans, etc. It is also said to relieve spasm of bladder and depress cough reflex like diacetyl morphine. But for obstetric analgesia, pethidine is to be preferred as amidone affects the fœtus undesirably. Under the trade name of dolophine hydrochloride it is available as an injection. A syrup is also on the market. The toxic effects so far observed after repeated use were dizziness, nausea, dryness of the mouth and occasional diaphoresis. Physeptone is used to wean morphine addicts. In cases of inoperable cancer as much as 30 mg. four hourly have been given.

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Another analgesic C.B. 11 or 4.4 diphneylmorpholino heptano[3] hydrochloride has lately made its appearance claiming to be of great use in pain of coronary thrombosis. In doses of 30-50 mg. orally, relief was obtained in 20-30 minutes and the effect lasted about 3-4 hours. Intramuscular administration of 10-20 mg. gave relief in 10-15 minutes while intravenous gave relief in 2 minutes. In the last instance there was a momentary feeling of dizziness which eventually passed off. The drug promises to be superior to pethidine and even amidone.

Yet another is N.V. 903 or 3.3. diethyl 2.4 dioxotetra hydro pyridine, but with a more pronounced sedative effect in addition to the analgesic action. In 0.4 G doses, sleep was induced with an effect equivalent to 0.1 G of pentobarbital. The sleep was induced in about half an hour and lasted 6 to 7 hours. There was no hang-over effect.

OBSERVATIONS ON LOCAL ANÆSTHETICS

An interesting observation has been made with regards ephedrine. Ephedrine when injected into the subarachnoid space in frogs showed evidence of spinal anæsthesia. When ephedrine was combined with procaine, there was potentiation of spinal anæsthesia which was thought to be secondary to vasoconstriction and prevention of diffusion of the spinal anæsthetic. Ruben (1948)[11] actually operated on man under spinal ephedrine. Intrathecal ephedrine had no effect on blood pressure, suggesting thereby that only a negligible quantity was absorbed into general circulation. It is therefore to be concluded that intrathecal ephedrine is of no avail for vasopressor effect. These findings are remarkable instances of a drug intended to have a particular effect not producing it while an unexpected effect was there which was none the less welcome.

Another pharmacological observation hitherto unnoticed has come to light. When intravenous saline by drip method is administered to cases of shock or reduced blood pressure or dehydration, difficulty is often encountered in the rate of flow of saline or any other fluid substitute. This is most often due to venospasm.

When 1 per cent. procaine 5-10 c.c. is then injected slowly, the rate of flow of saline improves. This is probably due to opening up of the veins by relaxation of the vein wall by a local action of procaine on the vein. The effect seems to last from 20-45 minutes. The procaine injection could be repeated after an hour to produce similar effect. This is a simple nevertheless a valuable observation.

MIGRAINE—"OCTIN" AND "D.H.E."

Octin is an ergotamine substitute called also methyl iso octenylamine. In doses of 100-200 mg. orally, octin gave prompt relief in migraine. When patients anticipate an attack, self medication by subcutaneous injection is permissible. The drug seems to act as a mild stimulant of the sympathetic system causing contraction of blood vessels and also as a relaxor of plain muscles. The action of sympathomimetic-sympatholytic drugs in relieving migraine has always been a puzzle. With octin, individual variations are occasionally noticed like high rise in blood pressure, palpitation, dizziness and occasionally syncope. A preliminary test dose of 25 mg. should be given for observing possible sensitivity. Many patients seem to prefer octin to ergotamine as octin does not cause nausea, cramps and other peripheral vasoconstrictor effects.

Hence an improved product called dehydrogenated ergotamine or D.H.E. is on the market claiming to be free from the delayed toxic effects of ergotism and the ecbolic action.

TRIGEMINAL NEURALGIAS AND ANTIHISTAMINE DRUGS

When on the subject of analgesics, one may be permitted to refer to a new conception of the etiology of trigeminal neuralgias and their treatment. The seasonal occurrence of trigeminal neuralgias associated with other ailments incidental to seasonal changes, crops and their harvest, suggested an allergic factor in the etiology of trigeminal neuralgia. Experimentally, in pain-free periods administration of histamine produced typical neuralgic attacks in many patients with this diathesis. On the assumption therefore that allergy plays a large part, antihistamine drugs were tried with remarkable effect in controlling the attacks. That the spasmolytic and sedative actions of benadryl were not responsible for the relief of pain has been shown by further observations that atropine and phenobarbitonum did not give relief under similar conditions. We welcome more data in corroboration of this theory.

A NEW SPASMOLYTIC—PARAPANIT

A new spasmolytic called parapanit or diethylamino ethyl ester of phenyl cyclopentane carbonic acid from Swiss laboratories has come to us. This compound seems to combine the spasmolytic properties of atropine on the one hand with those of papaverine on the other. In disorders of the extrapyramidal system, the action of parapanit seems to consist in a direct depressent action on skeletal muscles and deep sensibility manifestations. In optimum doses its therapeutic effect could be obtained without the parasympatholytic effect. When subcutaneously administered, relief to tremors of Parkinson's disease is obtained in a few minutes, the effect however gradually passes off. Hence a scheme of gradual and evenly spaced regimen is needed. Parapanit was also found useful in rheumatic affections of the joints in 0.05 G doses administered five to ten times a day for about a week. Decreased muscular rigidity and increased joint movements were observed. As with anticonvulsants it is advised not to precipitately switch over from one drug to another, in this case say from stramonium to parapanit.

Diparcol is a French equivalent to Parapanit.

As, a fortis (strong) and a mitis (weak) compound of parapanit are available, medical men using parapanit are enjoined caution with regards dosage instructions to their patients.

ANTICONVULSANTS

Ketogenic diet was proved effective in many cases of convulsions in children. This makes us pause to think if we had needlessly indulged in costly anticonvulsants with varying degree of toxicity.

The recent anticonvulsant Mesantoin which has proved fairly useful in epilepsy and other seizures, in addition to recognised toxic manifestations like overgrowth of gums, hair, gastritis, etc, showed alarming skin reactions over a protracted period, even after stoppage of the drug. As with tridione, blood changes are possible and hence frequent blood examinations are necessary when using the drug.

ALCOHOLISM—A NOVEL TREATMENT

Chronic alcoholics have been treated so far by psychological methods with indifferent results. "Antabuse" or tetra acetyl thiuramidisulphide is a new drug said to sensitise the tissues to alcohol and produce a train of symptoms like dilatation of facial vessels, raised heart rate, discomfort, uneasiness and increased pulmonary ventilation. By these symptoms, the addict is made to develop a disgust for alcohol, even the smell of it.

Antabuse is administered in doses of 1-1.5 G followed by 0.5 G daily and this suffices to produce the discomfort when alcohol is taken subsequently, the discomfort developing into a disgust leads to desist from drink. The action seems to be due to the production of acetaldehyde, a large proportion of alcohol being readily oxidised and normal elimination as carbon dioxide being blocked. This has been experimentally verified by administering continuous intravenous acetaldehyde to normal individuals who experience similar train of symptoms as those who took alcohol after antabuse.

CURARIFORM DRUGS

Curara in general is said to act on skeletal muscles by blocking the action of acetyl choline on motor end plates. Since smooth muscles in the gut and others like the uterus also appear to contract with acetyl choline, it is to be expected that these muscles will also be 'paralysed' to some extent. Normally, doses that paralyse skeletal muscles may not affect smooth muscles, but one occasionally notices individuals whose smooth muscles are also affected. But this apart, a train of symptoms is noted in patients who receive either 'intocostrin' or 'd tubocurarine' *i.e* a transient fall in blood pressure with subjective symptoms of headache, giddiness, warmth etc. Experimentally, when curarine is injected into the skin, the triple response of Lewis is noticed, the trauma effect not being responsible. Intra-arterial injection of curarine caused augmentation of hydrochloric acid in the stomach. The suspicion of release of histamine was confirmed partially by the other symptoms being abolished by antihistamine drugs like benadryl, pyribenzamine, etc. Though in experiments, intra-arterial injection of curara revealed evidence of histamine liberation, occasionally in susceptible individuals, intravenous injection can also produce symptoms of histamine release. Certain diseases like myasthenia gravis were particularly sensitive to curara, to a less extent amyotrophic lateral sclerosis. On the other hand cases of spastic paraplegia stood enormous doses of curara without any untoward effect. These observations just emphasise the need for caution in the use of curara derivatives and the use must be in the hands of expert anæsthetists.

VEGETATIVE NERVOUS SYSTEM AND TETRA ETHYL AMMONIUM SALTS

Tetra ethyl ammonium bromide was put into use in hypertension to reduce blood pressure by a sympatholytic action on the ganglion cells. Subsequently it was noticed that not merely were the sympathetics ganglion cells paralysed, but the parasympathetic counterpart were also influenced. There was not only fall in blood pressure (by a sympatholytic effect) but also reduced secretions as a whole, paresis of the gut, atony of the bladder etc. Evidence is accumulating to show that tetracthyl ammonium compounds act as regulators of the vegetative nervous system with a - double edged action. Experimentally the heart rate is augmented in animals whose heart has been slowed by morphine and slowed in animals whose heart rate has been augmented by barbiturates. Clinically, in cases of tachycardia due to hyperaction of the sympathetics, intravenous injection of 2 c.c. of 10 per cent. T. E. A. B. once a day for three or four days reduced the pulse rate appreciably. On the other hand in asthma and bradycardia, repeated injections of T. E. A. B. produced a progressive acceleration of the pulse rate, bringing the rate round about to 75 per minute.

In some cases of sinoauricular block, intensive ephedrine therapy had no effect on the heart interruption while 3 c.c. of 10 per cent. T. E. A. B. administered intravenously caused the disappearance of the block. The block however reappeared after about three hours.

This is a new conception of a regulating mechanism in the ganglion cells; its relation to acetyl choline which functions at the preganglionic level the esterase, histamine, curarine, prostigmin etc. await elucidation. But one should not forget that tetra ethyl ammonium compounds may differ in action profoundly among themselves, the chloride from the bromide, the ammonium ion being prominent in some (convulsant) or sometimes resembling curarine, sometimes nicotine; in general the action being unpredictable. Till knowledge regarding the regulating mechanism at the ganglion level clarifies, the clinical utility of T. E. A. compounds is nil. No one should handle a medicament whose effects cannot be reasonably anticipated.

CIRCULATORY SYSTEM

DIGITALIS

The optimism of one American school regarding single dose digitalisation of the heart with digitoxin, the purified crystalline glycoside, is being assessed by many cardiologists. Some modifications in the original scheme of Gold (1946)[12] has been suggested. Medical opinion is still in favour of oral administration of digitalis preparations, even digitoxin. Parenteral route may be imperative in pulmonary œdema following acute left ventricular failure, in some cases of auricular fibrillation with rapid ventricular rate and in patients with sinus rhythm when excessive vomiting is associated.

The conservative school to which belong many British cardiologists prefer the powdered leaf to the purified glycoside though the purified glycoside is more reliable for the uniformity of potency, freedom from local toxic action when given orally etc. Regarding dosage the 1.2 mg. single dose of digitoxin for complete digitalisation was not so satisfactory. At least 2 mg. in the aggregate are needed, but this need not be administered in a single dose. Like the Eggleston scheme for Tro Digitalis, a gradual decreasing dose of 0.8 mg. followed in four hours by 0.5 mg. then a 0.3 mg. after another four hours seem to serve the purpose. The daily maintenance dose remains at 0.1 or 0.2 mg.

Some cardiologists have noted abnormal rapid rhythm as a toxic manifestation of digitoxin occurring more frequently than with the leaf preparations. With the powdered leaf preparations, prodromal symptoms of nausea, vomiting serve as a warning, but with digitoxin the warning signals are absent, the abnormal rhythm being the first sign of digitoxin intoxication. Hence each preparation seems to have points for and against.

The fact that seems to emerge out of these discordant findings is that no hard and fast dosage scheme is possible for digitalis therapy. Each failing heart has to be medicated according to its needs and response—for "No two matchsticks are alike".

The duration of treatment of a 'potential' failing heart with digitalis has engaged the attention of some. Digitalis, some cardiologists feel could be administered for the rest of the life of such a patient like substitution therapy with insulin or liver. Cardiac enlargement and dilatation a manifestations of a failing muscle and under the influence of digitalis, according to them, the myocardium could be made to retard enlargement. This seems to suggest that digitalis supplies some unknown nutrition (calcium) ? to heart muscle directly or indirectly, thereby conducing to an efficient cardiac structure and function. But this view should not make clinicians oblivious of the chances of digitalis intoxication. Digitoxin acts slowly and is slow of dissipation; cumulation is therefore to be expected.

QUINIDINE

In many heart conditions, there is evidence of better effect when digitalis and quinidine are administered simultaneously. Early work of Lewis showed that dihydroquinidine, an alkaloid present in commercial quinine was more effective in auricular fibrillation than quinidine. During he war, the National Research Council compared the findings of Lewis and extended it to show that dihydroquinidine was also able to prevent ventricular fibrillation in experimental animals.

Fagarine, an alkaloid obtained from a plant indigenous to Argentine, has been reported to be a good substitute for quinidine. After a single dose of 0.1G of fagarine hydrochloride, normal sinus rhythm was restored, spontaneous auricular fibrillation being abolished.

ANGINA PECTORIS

Interesting observations have been made on the relation between anginal syndromes and thyroid function. Total thyroidectomy produced striking results in several cases of angina. Thiouracil, the medical substitute for surgical treatment, had also a similar effect. Depression of basal metabolism by 6.-propyl-thiouracil relieved substernal pain in many cases of hypertensive angina for a period of six months or more. Often it is not necessary to depress the B. M. R. to myxœdema level. In those cases where improvement did occur, it was within a period of 4-6 weeks of commencement of treatment. In doses upto 200 mg. a day for a period of two months, 6, propyl thiouracil did not show cognisable toxic manifestation.

Another interesting line of treatment of angina has come to light. Like quinine compounds relieving auricular fibrillation unexpectedly when given to malarial patients, pyribenzamine when administered for contact dermatitis, relieved patients with hypertensive angina of substernal pain. When further observations were made on similar conditions, all the patients were able to notice that their exercise tolerance was considerably improved. Patients with anginal syndromes who experienced substernal pain when crossing a room were now able to walk upstairs to 2nd and 3rd floors without experiencing pain (Mandelgaum 1948)[13]. The *modus operandi* of an antihistamine drug in angina needs elucidation. Khellin, an extract of the seeds of Ammi visnaga, an eastern Mediterranean plant, has been reported by several Egyptian cardiologists to be effective in angina. In doses of 100 mg. administered orally or intravenously B. D. relief was obtained in angina for a prolonged period. Cases that were resistent to aminophylline responded well to khellin. The drug was not contraindicated in hypertension. (The preparation unfortunately has not been standardised satisfactorily.)

CORONARY THROMBOSIS AND THEOPHYLLINE WITH ETHYLENEDAMINE

Aminophyllin is being widely used as a coronary vasodilator. It is also thought to be a cardiac stimulent. On injection the action is rapid in onset. But is stimulation of the heart in a patient with recurrent coronary thrombosis desirable? Sometimes untoward complications, even sudden death is possible in a heart subject to stimulation when suffering from a handicap of diminished blood supply to the myocardium. Its utility in the maintenance therapy of a cardiac sufferer is also to be proved. Abdominal discomfort when aminophylline is orally administered is not infrequent.

VASODILATORS

Papaverine relaxes many smooth muscles, in particular those of the blood vessels. In angina pectoris and myocardial infractions, papaverine tends to enhance the coronary blood flow. Its capacity to relax vessels is particularly marked in reflexly constricted vascular channels.

Evidence is coming to show that papaverine relaxes cerebral vessels that are in spastic condition. Several encephalopathies associated with hypertension and cerebral vascular disease without hypertension seem to respond to papaverine. In doses ranging from 2 grains to 18 grains a day, papaverine shows no side effects. Some patients who had been taking about 9 gr. of papaverine a day, for two years, showed no deleterious effects. Papaverine synergises well with phenobarbitonum while being partially antagonised by coffee and tea.

VASOCONSTRICTORS

Once again a note of caution is sounded in the indiscriminate use of vasoconstrictors for rhinitis and nasal turgescence. Daily and systematic use of nasal drops and inhalents by some is being noticed. They are expected to relieve congestion and give immediate relief to nose blocking; this they do.

But the healing process is delayed and in some cases fraught with grievous side effects. The side effects may be either sinus or ear complications, sometimes extending to higher regions of the brain. Privine drops seem to be the worst, next endrine and to a less extent benzedrine and tuamine. All these have a place in symptomatic cold treatment but are not to be deemed a prophylactic or cure for regular indulgence.

HÆMOSTATICS

Physiologists have done enormous work of late in trying to provide surgeons with efficient hæmostatics. Local styptics of the vasoconstrictor type, coagulants of the astringent group have had their day. Manipulations have been made with prothrombin, thrombokinase, calcium factors of clotting mechanism to help surgeons to tackle the annoying bleeding. Today physiologists are forging a new weapon with fibrin and thrombin or allied substances for a more direct aid to clotting and preventing hæmorrhage. Such substances after executing their task of arresting hæmorrhage by clotting and 'sealing' the area if left alone get absorbed with no serious consequences. Fibrin foam, fibrin film, gelatin sponge, alginic acid, oxidised cellulose etc. are used as packing material in operations. These after effectively closing the vascular breaches, remain on the spot after operation and could either be removed after some time or if left alone get absorbed without any unwanted effects. Problems relating to their sterilisation, protein shock, idiosyncrasies or sensitisation are being faced and combated by physiologists. Surgeons eagerly await this perfected weapon in their hands ere long. (Those interested in this subject are referred to "The Experimental studies on hæmostatics" by Frantz V. published in the Annals of Surgery 127—p. 1165 June 1948).

ANTIHISTAMINE DRUGS

A galaxy of newer antiallergic or antihistamine drugs are available today. Combinations of antihistamine drugs with others like privine are also available.

Aleudrine has been found useful in asthma and with a mild cardiac stimulant action. Sometimes it tends to cause palpitation.

Theophorin, another antihistamine drug, originally known as N. U. 1504, is a polycyclic amine belonging to a group of compounds hitherto unfamiliar.

Theophorin has the formula $C_{19}H_{19}N_2$ methyl 9 phenyl tetra hydro 1 pyrideidine and promises to be useful in œdematous conditions where some H. substance is thought to be the causative factor. It has also sympatholytic properties. Patients who are not amenable to benadryl respond to theophorin ; the dosage of the latter being half of benadryl and without any side effects.

Two halogen derivatives of anthisan named Chlorothen and Bromothen show an interesting anti-adrenal action in addition to antihistamine properties.

Decapryn succinate is yet another antihistamine compound. Experimentally it antagonises about all the histamine effects in animals like bronchospasm in guinea pigs (even when administered as ærosol) 200 m. l. d. of the pressor effect on rabbit's vessels, whealing reaction in all cases and capillary permeability in all animals. Like many other antihistamine substances it has local anæsthetic properties, drowsiness, as a side effect even in therapeutic doses of 25-50 mg. Individual susceptibility is not infrequent.

Neohetramine, another antiallergic substance, is a methoxy derivative of an earlier compound called hetramine and is the pyramidine isœster of neoantergen. It claims to be comparatively free from the serious side effects of others.

Some so called antihistamine drugs have in addition varying degrees of sympatholytic or sympathomimetic action, antiacetyl choline and of course local anæsthetic action. Some show antispasmodic and as already observed quinidine-like action.

Experience with antihistamine drugs in general shows that individuals evince a wide variation in clinical response. Hence a wide assortment is welcome. Their utility as a whole is fairly definitely demarcated. In conditions of skin and mucous membrane vascular phenomena, urticaria, they have a definite place not to mention vasomotor rhinitis, skin sensitivity reaction specially after penicillin, sulpha drugs, liver etc. In serum sickness the cutaneous symptoms improve but not pyrexia and arthralgia. They don't seem to have a place in asthma or in any deep seated allergic states like migraine, arthralgias etc.

HÆMATOLOGY

ANTIPERNICIOUS ANAEMIA FACTOR

Data are now forthcoming for the claim of isolation of the antipernicious anæmia factor (A.P.A.) from liver extract. It is designated B12. In doses of 3-6 micrograms (a microgram is 1/1000 of a milligram) there is a prompt reticulocyte response. Patel, J. C., (1948)[14] noticed a very good response in cases of pernicious anæmia with a single big dose of about 80 micrograms. This A.P.A. factor is about 2,000 times as potent as folic acid. Adequate doses for a short period produce good results in severe magalocytic anæmias. The peculiar interest attached to this new potent A.P.A. factor is that it is said to be cobalt co-ordination complex and is red in colour. Cobalt is an essential trace element like copper and manganese and it has been known to prevent and cure anæmia of ruminants due to feeding pastures deficient in cobalt. Now that folic acid is not thought to be the A.P.A. factor of liver, if B12 is the real one, it should not only restore to normal the blood picture in pernicious anæmia but should also prevent cord manifestations and even produce some benefit in established neurological changes by helping the nervous system to recover its function. We await substantiation of this claim. (It may be of interest that to obtain one gram of this A.P.A. factor, no less than FOUR TONS of liver are needed.) The quest is at least 20 years old.

Like crystalline digitoxin obviating the necessity for biological standardisation, this crystalline A.P.A. factor may obviate the necessity for a tedious and unsatisfactory 'assay' on patients suffering from pernicious anæmia.

These findings on the new alleged A.P.A. factor also help to clarify prior observations that thymine folic acid and B12 were more or less similar and that the difference was merely quantitative; folic acid was deemed a thousand times more powerful than thymine and B12 as much more powerful than folic acid. We await more information on B12.

IRON DEFICIENCY ANÆMIAS

In anæmias due to iron deficiency when optimum iron by mouth was not tolerated, saccharated iron oxide, soluble in 2 per cent. strength has been administered with very good results. Five c.c. contains about 100 mg. of metallic iron. A dose of 500 mg. causes a rise of about 20 per cent. hæmoglobin.

AGRANULOCYTOSIS

This fearful condition which came in the wake of newer therapeutic agents like the sulpha drugs, gold, arsenic, thiouracil, etc., was till now a case of 'cure worse than the disease'. But with folic acid and penicillin, the fear associated with the condition is fast ebbing. Pentanucleotide compounds were once the mainstay for it. The role of penicillin here still remains obscure as so far there is no known stimulant action on leukopoiesis. Pyridoxine seems to be a valuable adjunct to the others in restoring leukopoiesis. Between folic acid and liver extract, the latter is to be preferred.

GAMMA GLOBULIN

The inclusion of this subject under hæmatology is open to question. Gamma globulin or immune serum globulin is a concentrated solution of the antibody fraction of pooled normal human plasma. It is used as a passive immunising agent against infectious diseases like measles, German measles, infective hepatitis, chickenpox, mumps, poliomyelitis, whooping cough, scarlet fever, etc. Functionally important plasma proteins are sorted out into groups, each with an important physiological activity of the plasma. These include fibrinogen, fibrin film, fibrin foam, antihæmophilic globulin, thrombin, serum albumin and gamma globulin. Gamma globulin is packed in 2 c.c. ampoules equivalent to about 50 c.c. of pooled normal plasma as 16.5 per cent. protein solution in glycine. Ninety per cent. of the protein is gamma globulin. It contains only those antibodies present in the plasma normally which will act against those diseases for which antibodies are present in adequate amounts. One cannot say if this therapy is different from immune sera therapy without immunising an animal.

HORMONES

The inter-relation of hormones with one another has been known for some time, one hormone reinforcing or nullifying the effect of another. Data has been presented lately for a relationship between insulin and œstrogenic hormones. Daily insulin dosage could be appreciably reduced by stilbœsterol. Oestrogens probably indirectly depress the diabetogenic secretion or activity of anterior pituitary with the result that œstrogenic therapy could be coupled with insulin for better action of the latter in diabetes.

DETOXICANTS

BAL

Reports of wider fields of detoxication by BAL are forthcoming. Arsenical dermatitis and agranulocytosis seem to respond to BAL therapy. Dermatitis and blood complications after gold therapy also respond well. Poisoning by corrosive sublimate or other mercurials are alleviated by BAL.

In animals, toxic effects of nickel, cadmium, chromium and antimony are also antagonised by BAL. Doses of 0.3G in 10 per cent. solution I. M. followed by half the dose in the next 12 hours and continued till a total of 1-3G in 4-5 days seem to serve the purpose.

Two more valuable facts have also come to light regarding BAL therapy. Preliminary administration of BAL as a precaution against possible toxicity of arsenic in therapy of syphilis (Mapharside) tended in a large measure to neutralise or nullify the curative action of the arsenical. On the other hand a 'mapharside-BAL' coupled compound readily kills some protozoa like the trypanasomes, BAL by its solubility acted as a carrier of arsenic into the parasite and thereafter by dissociation enabled the arsenic to attack the parasite while the BAL remaining out as a guard acted as an antidote in the reverse. In other words, the coupled arsenic-BAL compound enables the arsenic to attack the parasite and prevents the body tissue being invaded by the arsenic. If this finding is corroborated, arsenic therapy of syphilis will be rendered absolutely safe, the fangs of arsenic being removed and the stings left for therapeutic action.

Again, carcinogens like 3.4 benzpyrene are said to get fixed to the-SH groups of cells and hasten cellular metabolism. Could BAL exert a preferential action on the carcinogens and delay tumour formation? Lasky *et al.* (1948)[15] have shown that after repeated application of benzpyrene to skin of mice, 82 per cent. of control mice had developed skin tumour as against 58 per cent. of mice that were applied both BAL and benzpyrene. Here is a new venture for BAL.

CONCLUSION

One may be permitted in conclusion to offer two words by way of suggestion to general practitioners for whose benefit these are written. First, general practitioners are expected to weigh the hazards of a drug against the hazards of a disease. In a critical or urgent condition, the physician may be justified in taking a risk for his patient through the use of a drug about which he is not certain or clear. A gamble to save life may be pardonable. But an efficient and economic medical man would apply some time to the study of fundamental principles governing the action of a new drug before venturing to handle the same.

Second, the so called research in medicine or contribution to the sum-total of medical knowledge need not always be from a 'well equipped research lab' or from a big modern clinic. In the field of observation, chance favours only the mind which is prepared. A general practitioner is expected to be prepared by keeping himself moderately informed of current trends and events in the domain of medicine. With that foundation, a careful observation and record and follow up will greatly help him to make great contribution to the progress of medicine. One cannot do better than illustrate from the lives of two eminent general practitioners who contributed not a little to medical knowledge. Jenner was an apprentice to a country doctor in Gloucestershire. He casually overheard a remark by a pretty milkmaid with proper pride in her youth beauty "I shall never have an ugly pockmarked face like you—I've had cowpox". We know the subsequent events. The remark of the milkmaid was a seed that fell on a prepared soil that was equipped with current medical trends.

Again, James Mackenzie was a partner in practice in Burnley in Scotland. His ambition was just to make himself a better doctor, the idea of research never entering his head. Says he in his biography "... about 1833, I resolved to begin a series of careful observations, entirely for my own improvement, never dreaming of research, for I was under the prevalent belief that medical research could only be undertaken in a laboratory or at least in a hospital with all the appurtenances." He took notes of all his patients and then decided to narrow it down to those whose signs and symptoms were connected with the heart. That was where general practice came in. A continuity is possible in general practice—not in institutions. He made one mistake under a common delusion. He left Burnley and went to London to join a "Big research institute", thereby breaking the continuity. A little later he realised his mistake, quietly withdrew himself from London to semiretirement in St. Andrews, Scotland where he regained something of the atmosphere of his general practice days. His contribution to our knowledge of heart diseases is because he was a general practitioner with a requisite foundation, careful observation and continuity. The lives of these are commended to general practitioners for emulation.

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THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

A. Karmally *

In the past, the treatment of subacute bacterial endocarditis has been a serious challenge to the medical profession; practically 99 per cent. died sooner or later with older methods of treatment. Lichtman[19] in a study of 2,500 cases of the disease recorded only one per cent. spontaneous cure of cases of subacute bacterial endocarditis. With the advent of chemotherapeutic drugs and antibiotics, a definite change in the outlook has occurred and cases have been recorded where the disease has been sometimes fairly well controlled and cured. This article is limited to a particular variety of endocarditis which is known as subacute bacterial endocarditis. The acute bacterial endocarditis met with in the course of primary septicæmic diseases like meningitis, pneumonia and streptococcal infections is not referred to here as it occurs in the course of a primary disease and the treatment is that of the primary condition..

Subacute bacterial endocarditis is a clinical entity characterised by a slow, progressive, downhill course with prolonged intermittent pyrexia associated with rigors, chills, sweating and embolic phenomena and with signs of cardiac involvement. It is caused by organisms of low virulence. In about 95 per cent. of cases the causal organisms are non-hæmolytic streptococci, various species of which are the normal inhabitants of the oral cavity and of the gastro-intestinal tract of man. Many of these species produce a greenish discolouration when grown on blood agar. Such organisms have been referred to as streptococcus viridans (alpha streptococci). Other species are indifferent streptococci known as gamma streptococci and they produce no change when grown in blood. *Streptococcus viridans* rarely affects a normal healthy endocardium. A damage to the endocardium either by rheumatic infection or a congenital malformation can be said to be a pre-requisite for subacute bacterial endocarditis. Valves damaged by syphilis or still rarely by arteriosclerotic changes may be involved.

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DIAGNOSIS

For successful treatment the diagnosis of subacute bacterial endocarditis should be established. This should be done as early as possible as an early successful treatment will prevent progressive myocardial as well as valvular damage leading to congestive cardiac failure, a not too infrequent complication which may terminate in death inspite of controlled infection.

For an early diagnosis, awareness of its possible existence in a given case is an important factor. Unexplained pyrexia especially in association with a rheumatic or congenital heart disease should arouse the suspicion of subacute bacterial endocarditis. Christian[8] has rightly urged that in any patient with valvular heart disease who has fever lasting more than a week that has not been fully explained, the diagnosis of subacute bacterial endocarditis should be strongly suspected.

The diagnosis can be made from the clinical manifestations of this disease which may be divided into three groups:

1. Toxæmia.—Fever, rigors, sweating, malaise, joint and muscle pains, loss of appetite, nausea, pallor.
2. Embolic phenomena.—Pain as the outstanding symptom in various areas where infarction occurs. Abdominal pain in cases of kidney and spleen infarction, paralysis from cerebral emboli.
3. Progressive valvular defects.—The changing murmurs in the valvular area with signs of circulatory insufficiency.

During the early weeks of infection the diagnosis is often difficult as pathognomonic stigmata of subacute bacterial endocarditis are frequently not present. Christian[8] has drawn attention to these early symptoms which may not be specific during the early phase of the disease. Malaise, fever, joint and muscle pains, nausea, loss of appetite were the early clinical manifestations in a large series of cases. In the majority of these cases the correct diagnosis was not made until the disease was moderately far advanced. The incorrect diagnoses that were entertained were influenza, grippe, typhoid, tuberculosis, undulant fever and acute rheumatic fever.

The diagnosis should be firmly established by the finding of the organism in a blood culture. This should be carried out before instituting treatment as the treatment may sterilise the blood stream. At least two blood cultures should be positive to substantiate the diagnosis and to eliminate outside contamination the blood culture must be positive on two occasions. It has been estimated that in 90 per cent. of cases presenting conclusive clinical signs of the disease, the causative organism is isolated in the blood stream. Multiple blood cultures, both aerobic and non-aerobic may be necessary before a positive result is obtained. Besides that of the usual venous blood, those of the arterial blood and bone-marrow are also recommended. Sometimes the blood may have to be taken several times a day when one sample may be positive. Cultures should be observed for at least 2 weeks before being declared negative. Blood may be collected at the time of their temperature spikes when it is more likely to be positive. However, it is well-known that in 10 to 15 per cent. of cases blood cultures are repeatedly negative although at autopsy organisms may be readily cultured from the vegetations on the valves. These are called "bacteria-free" cases. Two explanations are given to explain the non-existence of bacteria in bacteria-free cases. One is that the high concentration of antibodies usually present in the disease kills the bacteria as soon as they are swept out into the systemic circulation, the organisms in the vegetation being protected by the surrounding meshwork of the fibrin. The second is that they are so few that they escape detection in the blood culture. The diagnosis of bacteria-free cases must be made from clinical signs and recognised so as to institute early treatment.

TREATMENT

The treatment of subacute bacterial endocarditis may be reviewed in three stages: the earlier era, the chemotherapeutic era and the antibiotic era.

Earlier Era.—There was no specific treatment for this disease either by drugs, vaccines or serum. Drugs like salicylates, arsenic (as sodium cacodylate, arsphenamine) and all kinds of antiseptic preparations were given by mouth or parenterally like gentian violet, mercurochrome, iodine. Vaccines and sera failed. Kurtz and White[17] report a case where 1,800 c.c. of blood, 600 c.c. from each of three immunised donors, was transferred to the patient after removing 1,000 c.c. of patient's own blood with no result. The failure was explained as probably due to the higher titre of immunised bodies in the patient's blood than in the donor's blood, or the donor's artificial vaccination was less intense and was for short duration. Antibody formation by production of a sterile abscess also proved futile. Blood transfusion had often failed. Sometimes temporary improvements occurred when small repeated transfusions were given with due care. Physiotherapy had also been used in the shape of baths, ultra-violet or infra red exposures, diathermy, hyperthermia but was usually of no avail.

Chemotherapeutic Era.—With the advent of sulfonamides, numerous trials were made with prontosil, neoprontosil, sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine. The number of apparent recoveries were very few. White and Evans[33] reported 5 recoveries among 67 treated cases from 1939 to 1942, in contrast with the former Boston figures of only one recovery among 250 cases.

Adjuvant measures to sulfonamide therapy were introduced when it was found that the results were not gratifying. The first drug was heparin, an anticoagulant. Kelson and White[16] used it in conjunction with sulfonamide in the treatment of 7 cases ; only one was alive 5 years later. Simultaneously Friedman, Hamburger and Katz[10] used heparin alone in a case without any benefit.

Following White and Parker's[32] observations that in vitro sulfonamides were more effective against bacteria when incubated at higher temperature for a number of hours, Solomon[31] introduced hyperthermia as an adjuvant to sulfonamide therapy. He used typhoid-paratyphoid vaccine by continuous intravenous drip in order to maintain a temperature of about 104°F. and recorded four apparent recoveries of from 2 to 18 months duration. Independently Bierman and Baeher[4] achieved sterilisation of the blood stream and recovery in 2 cases by hyperthermia. Solomon[31] reported 5 apparent recoveries out of 22 cases by this method, but this favourable response was not obtained by other investigators.

The results of treatment with sulfa drugs have not been very striking ; and one has to consider many factors in the problem of treatment of such an infection by sulfa drugs. These factors are : (1) It is difficult, wellnigh impossible, for the drugs to penetrate to the centre of fibrin clots containing bacteria. (2) Bacteria may become fast to the drug. Some strains of *St. viridans* are resistant from the beginning and therefore the relative sensitivity of the organisms should be determined before beginning the treatment. (3) Serious toxic effects of long continued large doses of the sulfa drugs and hæmorrhage due to anticoagulant drugs call often for a cessation of treatment.

Prior to the introduction of penicillin, the results in the treatment of subacute bacterial endocarditis by antibiotic drugs and sulphonamides have been summarised by Robert J. Glazer[13] as follows :—

TABLE I.

Results in the Treatment of Bacterial Endocarditis before the Introduction of Penicillin.

AUTHOR	Reference Number	Number of Cases	No Chemotherapy	Recoveries	
				Sulfonamides Only	Sulfonamides and Fever
Libman and Friedberg	10	111	4 (3.6%)		
Lichtman	8	2596	25 (1.0%)		
Kelson and White	11	246	0 (0.0%)		
Favour *et al*	9	237	0 (0.0%)		
Lichtman	8	489		21 (4.0%)	
Kelson	12	197		4 (2.0%)	
Galbreath and Hull	13	20		0 (0.0%)	
Favour *et al.*	9	39		0 (0.0%)	
Lichtman	8	102			11 (10.7%)
Favour *et al.*	9	16			4 (25.0%)

PENICILLIN THERAPY

With the discovery of penicillin numerous attempts have been made to study the effect of penicillin in subacute bacterial endocarditis. Earlier attempts probably failed because the doses used were small owing to the limited supply of penicillin. Keefer *et al.*[15] treated a small series of 17 patients with the small doses then available due to restricted supplies. The total amount of penicillin varied from 240,000 to 1,760,000 units and was given over periods ranging from 9 to 26 days. Of the 17 patients, 10 were unaffected, four died and only 3 showed improvement.

The first successful treatment of subacute bacterial endocarditis was reported by Loewe[29] *et al.* Their seven patients were treated by penicillin and heparin. They received from 1 to 4 courses of the therapy, the total amount of penicillin varying from 867,990 to 7,890,340 units. This optimistic report soon stimulated other attempts. The National Research Council through the Committee on Therapeutics released stocks of penicillin to various groups of investigators. Many favourable and encouraging reports have been contributed and now penicillin therapy of subacute bacterial endocarditis rests upon a strong foundation due to extensive clinical and laboratory research.

Treatment by Penicillin.—To successfully treat a case of subacute bacterial endocarditis early diagnosis and adequate treatment are necessary. The aim is not only to sterilise the blood of the organisms but also to destroy the organisms in the valvular area so as to ultimately heal the valvular lesion completely and avoid relapses.

Therefore a proper consideration of important factors as the penicillin resistance of the infecting organism, the effective route of administration, the dose, and the duration of the therapy should be arranged so as to procure a successful result.

Penicillin Resistance of Infecting Agent.—It is well known that penicillin is selective in its anti-bacterial action being quite potent against certain organisms and having little or no effect against others. Thus the best results would be obtained if the infecting agent of subacute bacterial endocarditis would be susceptible to penicillin.

Fortunately it has been shown that most species of non-hæmolytic streptococci are susceptible to penicillin. More than 90 per cent. of the organisms, so far tested, have been completely inhibited *in vitro* by concentrations of 0.1 unit or less of penicillin per c.c. Chain *et al.*[7] and then Abraham *et al.*[1] demonstrated that the organism *streptococcus viridans* was inhibited *in vitro* by the drug. A variation was noted in the sensitivity of several strains to penicillin. Libman[18] examined 50 strains of bacteria isolated from cases of subacute bacterial endocarditis and found a variation in penicillin sensitivity from ½ to 64 times as great as that of the test organism *Streptococcus hæmolyticus*, which is stated to be ½ to ⅛ as sensitive as the strain of *staphylococcus aureus* found in human infections.

The penicillin sensitivity of the infecting organism is an important guide to the dosage used in a given case. Bloomfield *et al.*[5] analysing the causes of failure in penicillin therapy found good evidence that a correlation exists between bacterial sensitivity in vitro and the patient's clinical response. One of the patients who was treated with 450,000 units of penicillin daily failed to respond; the infecting organism was shown to be insensitive to high concentration of the drug *in vitro.*

Although other factors must be taken into account a correlation exists between the *in vitro* resistance of the organism and the dosage of penicillin to be administered. In general, if the causative organism is inhibited by 0.05 units or less of penicillin per c.c. of culture medium, one would expect therapeutic success with moderate amounts of penicillin. If more than 1 unit per c.c. is required, the chances of success are greatly reduced. No hard and fast rules can be had. A dosage schedule producing a blood level at least equal to and preferably 5 times greater (Loewe)[21] than that necessary to inhibit the organism *in vitro* should be adopted.

Sometimes the *in vitro* determinations do not agree with the clinical response and one may have to begin treatment regardless of *in vitro* tests. Pearsall *et al.*[28] state that there appears little correlation between *in vitro* tests and response to penicillin. 6 of 10 cases with resistance upto 5 or more units per c c. were easily controlled by the usual programme of dosage. However they say that in all the difficult cases the bacteria were found to be highly resistant.

Route of Administration.—Penicillin administered orally is destroyed by gastric juice. It is not a method of choice, but the convenience of administration by the oral route is an attractive feature. Recently attempts have been made to overcome the action of gastric juice, by combining with various substances calculated to neutralise the destructive effects of the gastric juice. A number of substances have been used and promising results have been obtained with trisodium citrate, basic aluminium ammoniacetate, corn oil, lanolin, human plasma protein, raw egg white and sodium bicarbonate, aluminium hydroxide.

The blood levels obtained by oral administration of penicillin reach only about ⅓ to ⅕ of that obtained by intramuscular injection. It may be desirable to restrict this method for the sensitive penicillin organisms like pneumococci, and pneumonia has been successfully treated by large oral doses of penicillin given in the form of tablets. As subacute bacterial endocarditis is a protracted disease, and very large doses are required and at times the resistance of infective agent may be high, this route has not been used in cases of subacute bacterial endocarditis.

Parenteral Administration.—Subcutaneously penicillin is not given. The intravenous and the intramuscular routes have been used.

Intravenous Route.—It may be given intermittently or by a continuous drip. A continuous intravenous drip has been used and this method produces the desired high level. But there are many difficulties encountered in the intravenous administration of penicillin. One cannot carry out the technique in a patient's house and he has to be treated in a hospital. The frequent and common occurrences of thrombophlebitis at the site of injection precludes continuation of a treatment for a long time. In short acute infections the method is preferred but in subacute bacterial endocarditis one has to continue the therapy for a long duration of 4 to more weeks. Obstruction of the needle necessitates frequent changes of the intravenous drip and local infiltrations ruin the veins. Continuous daily intravenous transfusion of 1,500 to 2,000 c.c. of fluid may not be desirable when there is a tendency to heart failure. Thus the intravenous route with its manifold difficulties is not a popular one though it is still used mostly in the U. S. A.

Intramuscular Route.—By this route penicillin may be given continuously or intermittently. Continuous treatment has again the same difficulties, hospital and nursing facilities, pain at the site of intramuscular infiltration, œdema of the injected extremity and formation of penicillin abscesses.

Intermittent Administration.—This has been the most popular method because of its great convenience. The absence of thrombophlebitis, the ease and comfort of an intramuscular injection almost painless, avoidance of large volume of fluid, have contributed to the preference of this method. D. J. Anderson *et al.*[2] having used the continuous intravenous and continuous intramuscular methods state that they believe these methods do not offer any particular advantages, being difficult to regulate and result in a certain degree of immobilisation of the patient. They have found the intermittent intramuscular route as the most satisfactory and convenient method.

Objection is raised to the use of intermittent intramuscular route on the grounds that penicillin levels are not maintained and so effective concentration may not be obtained. The favourable and encouraging reports by this method in subacute bacterial endocarditis and acute infections seem to indicate that this is not an effective barrier to therapy provided the intervals are not too long. Thus the intermittent intramuscular method, because of its great ease and comfort, has been used in most of the cases.

DOSAGE

With regard to the dosage there are no fixed criteria by which one can be guided in the treatment of subacute bacterial endocarditis. The early failures of cases treated by pencillin were probably due to smaller doses. The treatment by smaller doses also may have given rise to drug fastness of the organism. Hence it is recommended to use initial large doses to render the blood sterile and the organism non-resistant. The schedule dosage recommended is 1,00,000 to 2,00,000 units of penicillin to be given intramuscularly every three hours. Though these doses seem to be excessive, experience has shown that better results would be obtained by starting a higher dose. The minimal dose should not be less than 50,000 units every three hours which could be increased to a lakh when the beneficial response within 2 or 3 days is not evident. Sometimes even with the big doses the response is not adequate. The use of so-called "booster" dose was suggested in the hope of facilitating penicilin penetration into the vegetations on the heart valves in bacterical endocarditis. The "booster" dose consisted of a single intramuscular injection of 50,000—3,00,000 units twice daily in addition to the usual therapeutic dose. These favourable results by "booster" doses were noted when the pencillin dosage was small ranging from 15,000 to 30,000 units every 3 hours. The drug being now freely available, 8 large doses each of 100,000 units or more are certainly much more desirable.

DURATION OF TREATMENT

Various different periods of treatment with penicillin subacute bacterial endocarditis are reported. A review of the studies on the use of penicillin in subacute bacterial endocarditis so far reported indicates wide variations in the duration of treatment. Dawson and Hunter[9] obtained remission of the disease in 5 patients treated for periods of only 10 to 14 days with doses ranging from 100,000 to 320,000 units daily. On the other hand, relapse after therapy occurred in 2 patients treated for 103 and 85 days, respectively. In the latter instance, the amount of drug administered in each was sufficient to maintain a blood level that would match the *in vitro* resistance of the infecting organism. Bloomfield, Armstrong, and Kirby[6] treated 11 cases of bacterial endocarditis for 8 weeks and concluded that the minimum period of therapy should be 2 months, or perhaps longer. Loewe[22] recommended a minimum treatment period of 5 weeks. Meads, Harris, and Finland[25] obtained recovery of 7 out of 9 cases treated by intramuscular injection every 2 hours for a period of 2 weeks. A lack of unanimity concerning the duration of pencillin therapy still prevails, although there has been a tendency to prolong treatment schedules with increasingly satisfactory results.

Bæher and Gerber[3] treated 25 cases of subacute endocar~~ditis~~ and, like other investigators, established an arbitrary period of treatment. It was found that in most instances, a 4-week period of pencillin administration sufficed to produce recovery from the disease.

In most instances a minimum period of 4 weeks and an optimum period of 8 weeks of treatment is effective. A careful evaluation of each case is essential so that adequate and early effective therapy may be instituted and progress of valvular damage avoided. Inadequate dosage of penicillin and unnecessary prolongation of treatment is uneconomical and may ultimately leave the patient cured of bacterial endocarditis but doomed to chronic invalidism or to an early death from congestive failure. No patient should be discharged from the hospital immediately after pencillin is discontinued. They should be watched closely for two or more weeks after the conclusion of penicillin therapy.

DRUG TOXICITY

The great advantage of penicillin therapy is the lack of toxicity of this drug, even when given for a long time and in large doses. With the purified penicillin now available the reactions to the drug are further reduced. Urticaria and skin complications are the common toxic symptoms besides cramps, sweating flushing, headache, fever and angioneuritic odema.

The local thrombophlebitis during intravenous administration is a troublesome complication necessitating a change of route of administration. In intermittent intramuscular injections pain at the local site is a frequent complaint but does not so much interfere with the treatment. The sodium salt is said to be least irritating.

ADJUVANT DRUGS

The use of heparin with sulphonamides though at first thought to be a useful adjuvant was ultimately found to have made no appreciable difference. The anticoagulants were used with a view to enable the antibacterial agents to reach the organisms embedded in the vegetations protected by a fibrin platelet barrier. The anti-coagulant prevents fibrin and platelet deposition and thereby permits sterilisation and repair of valvular infection. The after results by the anti-coagulants showed no appreciable difference and lately Moore[26] has shown that the vegetations are largely necrotic tissues and that growth does not occur by the addition of fibrin to the surface. Further Friedman[11] has shown definitely that penicillin diffuses equally through agar and fibrin clots showing that anti-coagulants are not necessary from this stand-point. Priest[29] in 10 patients examined could find no difference in the amount of fresh fibrin in the lesions of those receiving heparin or dicumarol from those not receiving such therapy. The high incidence of hæmorrhagic manifestations are a bar to this treatment. Fatal cerebral hæmorrhage may occur and cases of severe hæmaturia have been reported. Thus heparin and dicumarol have now been abandoned and not used in conjunction with sulfa drugs or penicillin. The use of certain other drugs, by competing with renal excretory mechanism, offers a better chance with good results as much higher blood levels of penicillin are obtained. Oral sodium benzoate 2 to 4 gms. every two to four hours, 12 per cent. sodium para-amino hippuric acid intravenously are given with a view to improve the penicillin levels. Recently caronamide in doses of 3 to 4 gms. orally every two to four hours has been used to increase the concentration of penicillin in blood with satisfactory results. It is thought to act by inhibiting an enzyme system of the renal tubules which excrete 80% of the penicillin.

The other supplementary treatment for the general condition of the patient should not be forgotten. The high caloric, high vitamin diet should be used. Blood transfusions of citrated blood or packed red cells should be given if anæmia is present. Hypnotic sedatives, iron, and laxatives should be used as indicated.

USE OF STREPTOMYCIN

Very few reports of cases treated by streptomycin are available. This antibiotic when given in large doses and for a long time produces damage of the eighth nerve resulting in vestibular and auditory effects which may at times be irreversible. Priest and McGee[30] have recently reported success with streptomycin in patients with streptococci highly resistant to penicillin and suggest that streptomycin might be of value when the causative agent is a gram-negative bacillus insensitive to penicillin. They used 500,000 units (0.5 gm.) per day but state that the dose must be adjusted in accordance with the needs of the patient.

CRITERIA FOR CURE

The question of a cure from subacute bacterial endocarditis is a difficult problem as enough follow up studies are not available. Longest period of follow-up observed has been for 2 years. At present the prognosis of subacute bacterial endocarditis should be extremely guarded for the first three months since most recurrences occur within this period. If the patient remains well during this period, the prognosis improves, and if he remains well for a year, one may safely assume that a recovery has occurred. Always the likelihood of a re-infection is present in these cases.

PROPHYLAXIS

Streptococcus viridans, the common infecting agent in subacute bacterial endocarditis, often affects the diseased endocardium as in rheumatic valvulitis and deformed valves due to congenital anomalies. A normal endocardium is rarely affected. It becomes our duty to prevent this infection occurring in individuals suffering from rheumatic carditis and congenital diseases. An adequate prophylaxis in patients with these underlying diseases would reduce the incidence of the subacute bacterial endocarditis infection. Horder[14] noted that in most cases the focus of etiological agent of subacute bacterial endocarditis was in the mouth. Libman[18] stated that *streptococcus viridans* is constantly entering the blood stream from various portals such as sockets of teeth, infected gums, nasal sinuses, the throat, and less commonly from infections in the ear, genito-urinary and gastrointestinal tracts. Okell and Elliott[27] found a transient non-hemolytic streptococcal bacteremia following dental extraction under general anæsthesia in 60.9 per cent of 138 cases, the frequency being considerably greater in patients with severe gum disease than in those with non-diseased gums.

Therefore, one has to be very careful in dealing with tooth extractions and minor operations on the oral cavity. It has been recommended to administer 2 gm. of sulfadiazine 2 or 4 hours before operation and 1 gm. every 4 hours for 48 hours after.

Another regimen is to administer 50 thousand units to 1,00,000 units of penicillin intramuscularly not longer than a half-hour before the projected operation and 25,000 units intramuscularly every 3 hours for 24 to 48 hours after.

RESULTS UP-TO-DATE

Undoubtedly with the advent of penicillin therapy results have been striking. As compared to one per cent. spontaneous recovery rate as stated by Lichtman[19] and the recovery rate of 3 to 6 per cent. with sulpha drugs, the results of penicillin treatment are very encouraging. Ten months after the first report by Loewe[23] *et al.* of 7 successfully treated cases, Loewe recorded a much larger group in which the original 7 were included. Of the 54 patients treated 16 died, a recovery rate of about 70 per cent.

The second large series of cases reported was that of Dawson and Hunter. They treated 20 patients, and reported 15 recoveries, 3 fatalities, and 2 relapses; the incidence of reported recoveries is 75 per cent. a figure nearly identical with that reported by Loewe. Out of another[12] series of 29 cases the recovery of 19 was recorded, with 6 fatalities, 2 of which were considered instances of controlled infection with death due to cardiac failure, and 4 still under treatment at the time of the report.

Strikingly similar results have been obtained by various writers. The follow-up data pertaining to cases followed longer than one year is insufficient to permit the estimate of those successfully treated. It is likely that, of these 70 per cent. results, the true recovery rate in the reported cases may approach to 40 to 50 per cent. a result which in comparison with the older methods is striking. Undoubtedly now penicillin holds the pride of place in the treatment of subacute bacterial endocarditis. In it we have a weapon which, if judiciously used in adequate doses and earlier in the disease, we may hope to save a large number of individuals who were before this doomed to certain death.

SUMMARY

1. With the advent of anti-biotic therapy notably penicillin, the treatment of subacute bacterial endocarditis has been revolutionised and one can offer in a good majority of cases a complete cure.
2. An early diagnosis confirmed by two positive blood cultures is a pre-requisite for the treatment of subacute bacterial endocarditis.
3. Determining Penicillin resistance of the infecting agent is not an absolute necessity for instituting the treatment as *in vitro* determinations often do not correspond with the *in vivo* results. In cases not yielding to penicillin the resistance may be determined.
4. The administration of penicillin by intramuscular route has been found satisfactory and convenient with good results. Sometimes intravenous route has to be resorted to. In dosage varying from 1,00,000 to 2,00,000 units 3 hourly, the treatment has to be prolonged and continued for a minimum period of 4 weeks to an optimum period of 8 weeks in cases which are very resistant.
5. The ease, comfort and the lack of dangerous complications make the penicillin therapy the treatment of choice.
6. Heparin and the use of sulphonamide drugs have not appreciably improved the results of therapy by penicillin only.
7. Up-to-date results have been satisfactory in over 50 per cent. of cases and if the patients remain well for a year one may safely assume that the recovery has occurred.

8. In rheumatic and congenital heart diseases one must prevent the complication of subacute bacterial endocarditis.

9. Tooth extractions and minor operations of infections round about the month should be with by a prophylactic course of sulphonamides or penicillin before and after the operations.

10. Thus penicillin therapy is the treatment of choice and in it we have a weapon which if judiciously used in adequate doses and earlier in the disease, can save a large number of individuals doomed to death.

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CURRENT MEDICAL LITERATURE

MEDICINE

THE TREATMENT OF SHOCK ACCOMPANYING MYOCARDIAL INFARCTION. WILLIAM B. SCHWARTZ, AMERICAN HEART JOURNAL, **33**: No. 2, 169-173, 1949.

William B. Schwartz reports of a patient with profound vascular collapse accompanying myocardial infarction, who was given 2,200 cc. of blood and plasma within a period of forty minutes. Recovery was rapid and uneventful. This massive transfusion was a life saving measure in this patient. Signs and symptoms of congestive heart failure did not develop.

The high incidence of shock or a shocklike state following coronary thrombosis is generally acknowledged. The manifestations include a precipitous fall in blood pressure, collapse, cold extremities, moist clammy skin, grayish pallor and unconsciousness. There is disagreement as to whether these clinical findings represent a true peripheral vascular collapse or the sudden development of cardiac insufficiency. The described shock picture is in marked contrast to the dyspnœa, pulmonary congestion, venous engorgement and œdema found in congestive failure.

If the sudden collapse of the patient was the result of "acute forward heart failure" then the heart was already incapable of handling the circulatory load, and it would seem that the additional strain of 2,200 cc. of blood and plasma intravenously should have hastened a fatal outcome. That instead he made a rapid and uneventful recovery would support the view that the failure was peripheral in nature and that restoration of the effective blood volume was the significant factor in his survival.

The foregoing facts suggest that in cases of myocardial infarction and shock without failure, it may be advantageous to treat this critical complication actively. Some authors feel that the use of plasma and blood is contraindicated in the presence of myocardial infarction. Probably cardiac decompensation may develop in some patients following such therapy, but it should be emphasised that this occurs in many cases without such treatment. If the peripheral circulatory collapse, in the absence of evident signs of failure, is not corrected, it seems probable that many patients will succumb immediately. With intravenous blood and plasma an appreciable number may recover.

The congestive heart failure that follows upon the increase in blood volume and the return of pooled blood to the effective circulation may be treated by venesection, digitalis, diuretics and fluid restrictions which would further aid the recovery of such patients who might have otherwise died in the acute shock phase.

Schwartz suggests that serious consideration be given to the use of blood and plasma in the treatment of shock accompanying myocardial infarction.

A. KARMALLY.

ORAL REACTIONS TO PENICILLIN. W. G. GROSS. B. M. J. **1**: 171-173, 1949. 14 refs.

Oral reactions to penicillin have been described by many. The author studied 59 cases. The two common conditions are discolouration of the tongue and stomatitis.

The discolouration begins 2 to 4 days after starting treatment and wears off in five to 14 days. The colour may be yellowish brown, brownish green, greenish black or black. The filiform papillæ are involved particularly in the central furrow and back: the tip of the tongue is free. With stomatitis there is a soreness of tongue and at times of the whole mouth and pharynx, with extreme discomfort on taking hot fluids, spiced foods and condiments. Sometimes there is agenisia and lack of salivation. The condition lasts for 6 to 10 days, and the loss of sense of taste for some weeks. The tongue appears red with bright-red prominent fungiform papillæ, and the normal fur is lost in a patchy manner. These effects have been ascribed to various causes—nicotinamide deficiency, base of the troche, but Gross does not think these play any part. But the reactions do not occur until there has been a complete change in the character of the oral flora.

G COELHO.

PARKINSONISM TREATED WITH PARPANIT. W. F. DUNHAM AND C. H. EDWARDS.

Lancet 2: 724-727, 1948 Fig. 1, Chart 1, Refs. 6.

Parpanit is a synthetic compound closely related chemically to antispasmodics like Trasentin and pharmacologically to atropine.

25 cases of parkinsonism were treated with parpanit. To assess and compare the similarity of parpanit with solanaceous drugs it was given to patients in following combination: (1) Solanaceous drugs and inert tablets; (2) Solanaceous drugs and increasing doses of parpanit; (3) Optimum doses of parpanit and solanaceous drugs gradually withdrawn; (4) Abrupt changes from solanaceous drugs alone to parpanit alone without the knowledge of the patient; (5) Inert tablets substituted for parpanit when it was being given alone; (6) Inert tablets substituted for parpanit when both the drugs are being given.

It was observed that, sometimes one, sometimes another drug was found to be more beneficial. Those patients which responded to solanaceous drugs also responded to parpanit. When parpanit was beneficial it was equally so whether it was given alone or in combination with solanaceous drugs. It was difficult for the patients to spot sudden changes from one drug to another.

Side effects of parpanit are similar to those of solanaceous drugs. They were giddiness, weakness, drowsiness and occasionally dryness of mouth, and blurring of vision. Beneficial effects rarely appeared before the side effects.

S. N. SHAH.

THE PERIOD OF TRANSMISSION IN CERTAIN EPIDEMIC DISEASES. R. E. HOPE SIMPSON.

The Lancet 2: 755-760, 1948. Fig. 2, Table 2, Refs. *nil*.

In the study of infectious diseases it is very important to determine the period during which a patient is infective to contacts and the variability of this period. These factors can be easily and reliably estimated by the study of serial interval that is the interval between the appearance of a particular symptom in one case and the appearance of some symptom in the case infected by him. To get reliable results this measuring symptom should be very carefully chosen and the hour for measurement should be fixed. If the incubation period is unknown its length and variability can be established by observing the serial interval in those secondary cases which had very brief and single exposure. If the incubation period is known period of infectivity and period of transference can be easily determined provided series is large and observations are accurate.

S. N. SHAH.

A METHOD OF TESTING ANALGESICS. RICHARD ASHER. The Lancet **2**: 771-773, 1948. Table 2, Refs. *nil.*

As psychological factors play a major role in the production and relief of pain, the results of many animal and human experiments and clinical trials are unreliable. Here a novel method was employed in assessing and comparing the analgesic properties of Veganin and Saridon. Veganin, Saridon and placebo tablets were made of identical size and shape and each had a different colour. The identity of colour was kept secret till the trial was over.

For any mild or moderate pain or ache two tablets of any colour were given and patient was requested to fill in a card stating the amount of benefit he obtained from the preparation. The result of this study showed that Veganin and Saridon are very effective in relieving mild and moderate pain, Veganin being slightly more so. In 80% of cases there was certain amount of relief. Inert tablets were able to produce similar relief in about 50% of cases. Women got much more relief from inert tablets than men did.

The investigation was fairly easy to carry out.

S. N. SHAH.

SURGERY

CARCINOMA OF THE LIVER—PRIMARY and SEONDARY, COLCOCK, B. P. Surg. Clin. N. America **28**: 673-678, 1948.

Primary carcinoma of the liver appears to be more common in Africa and China where an incidence of as high as 7.19 per cent of all autopsies has been reported. This may have something to do with the high incidence of infection with liver flukes, and the dietary deficiencies more common in these countries. In the U. S. A. an incidence of 0.66 per cent has been recorded by Webb.

X-Rays and radium are of no value in the treatment. But when the disease is limited to one lobe or part of a lobe resections have been carried out with occasional cures.

Secondary carcinoma of the liver. It is important to realise that occasionally what looks like a metastatic nodule in the liver on inspection during a laparotomy turns out to be benign after excision, either fibroma, scirrhous angioma, or small calcified cyst. Therefore a single nodule in the liver should not deter the surgeon from radical excision of an operable growth. Also, as Brunschwig has pointed out, a carcinoma of the stomach or colon adherent to the liver rarely infiltrates beyond Glisson's capsule which is an efficient barrier. Successful resections of solitary metastases in the liver lobes with cure have been recorded.

E. J. BORGES.

HYPERTHYROIDISM IN CHILDREN. ELMER C. BARTELS. The Lahey Clin. Bull. **6**: 68, Jan. 1949.

Medical treatment in these cases always results in relapses. Whereas formerly cautious multiple stage operations were necessary to obtain low operative mortality and morbidity in children, it is now possible after proper antithyroid treatment to proceed with subtotal Thyroidectomy in complete safety.

From 1943 to 1947 there were 12 children among the first 1,000 patients with hyperthyroidism to receive antithyroid treatment at this clinic in preparation for thyroidectomy.

Restlessness, irritability and greatly increased appetite are early symptoms. Rapid growth, increased body warmth and a palpable overactive heart beat were observed in many instances. Exophthalmos was present in 8 children and a visibly enlarged thyroid in all. The B.M.R. ranged between +21 and +63.

The preoperative treatment consisted of thiouracil in daily dosage of 300 to 600 mgs, or propylthiouracil, 100 to 200 mgs a day. It is essential to carry out this treatment until a return to a fairly normal state of health with a normal metabolic rate. Subtotal thyroidectomy was done in each case. The postoperative convalescence was uneventful in 10 cases. In 2 cases who had shown clinical signs of myxoedema before operation a tracheotomy was necessary to relieve respiratory difficulty from edema of the larynx.

Follow up studies reveal that 8 of the twelve children are in excellent health with an average B M.R. of —10. One patient has myxoedema and requires a daily dose of thyroid. One has a recurrent hyperthyroidism which is under control with Lugol's iodine.

E. J. BORGES.

PEDIATRICS

STIMULATION OF GROWTH IN BOYS BY SUBLINGUAL TESTOSTERONE THERAPY.

WILLIAM C. DEAMER. Am. J. Dis. Child **75** : 850-859, 1948.

The author treated five boys who were retarded in growth. Their chronological age was 14-¾, 14-¼, 14-¼, 10-½ and 8 years and bone age 9-½, 7, 11-½, 6-½ and 3-½ respectively. They were all given testosterone orally. Their gain in height at the end of one year of this therapy was 4.5 in., 2.9 in., 4.4 inches. 4.4 in. and 3.25 inches respecttively while their bone ages advanced 1-½ years in 9 months, 3 years in 20 months and 3 years in 18 months. Though the ultimate height was not increased " borrowing additional inches ahead of time was psychologically of great importance to these boys" The genital development was not abnormal, nor were there any behaviour problems.

G. COELHO.

TOXIC EFFECTS OF OVERDOSAGE OF VITAMIN D2 IN CHILDREN.

ROBERT DEBRE. Am. J. Dis. Child **75** : 787-791, 1948.

The author describes the clinical manifestations based on 21 personal observations Anorexia appears first, and may last for weeks. Sometimes it may improve for a little while but it will suddenly re-appear. With anorexia there may be nausea and vomiting and the latter appears with dramatic suddenness. Thirst is frequent and children get up several times at night to drink water. Intense constipation may alternate with severe diarrhœa. Other typical symptoms are pain in different parts of the body. If the condition is not checked in time the child becomes pale, has a worn look and sallow complexion, looses weight rapidly, becomes irritable, depressed and later indifferent to surroundings. There may be an elevation of temperature which leads sometimes to a wrong diagnosis. The blood pressure is raised so is the blood urea, calcium and phosphorus. There is a fall in the red cells and hæmoglobin, an increase in white cells and the sedimentation rate. All symptoms disappear quickly when the vitamin is stopped. Vomiting ceases in eight to fifteen days and once the constipation is relieved the child puts on weight rapidly. But the prognosis is not always favourable—2 out of 21 cases died.

G. COELHO.

ORALLY ADMINISTERED PENICILLIN IN PATIENTS WITH RHEUMATIC FEVER. B F. MASSEL, J. W. DOW AND T. D. JONES. J. A. M. A. **138** : 1030-1036, 1948.

Patients between the ages of 3 and 17 years, were studied with the object, beside others, of determining whether orally as well as intramuscularly administered penicillin could be effective in reducing the hæmolytic streptococcus carrier rate among ward patients, and whether the hæmolytic streptococcus could be eradicated from patients' throats by relatively infrequent administration of penicillin orally. Hæmolytic streptococcus carriers were given either 100,000 units or 200,000 units three times daily. Those with clinical or subclinical infections with hæmolytic streptococcus were given 200,000 units five times daily for 10 days. Amongst 37 patients who were observed permanent clearing of hæmolytic streptococci from the throat was effected in 28 patients. Prior to treatment 88 per cent of 229 throat cultures from 36 patients were positive to hæmolytic streptococci, but within 24 hours of treatment the incidence of positive cultures dropped to 24 2 per cent, in the next 24 hours to 5.9 per cent and during remaining period of therapy to 2.1 per cent. It was also observed that intramuscular injection was more effective.

G. COELHO.

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EPIDERMOID CARCINOMA OF THE CORPUS UTERI

P. N. Wahi* and R. L. Jain*

Primary squamous celled carcinoma of the corporeal endometrium is an unusually rare lesion. This is borne out by the fact that little detailed information exists in gynæcological texts except for a brief mention of the possibility of such a tumor. As far as I am aware, the tumor has been rarely discussed in literature, and its origin has always been a point of contention. Warren[9], in his 33 cases abstracted from the files of the Lahey Clinic did not report a single case of epidermoid carcinoma though he found 5 adenoacanthomas. Morrin[7], in his analysis of 88 cases of carcinoma of the body of the uterus, found all of them to be adenocarcinomata. Munro Kerr[8] has envisaged the possibility of a squamous epithelioma occurring in the corpus uteri derived from an upward spread of cervical cancer. He, however, points out that it may primarily commence in the body of the uterus when it is preceded by a metaplasia of the columnar into squamous epithelium. Curtis[1] has included in his classification of uterine carcinomata, the squamous cell carcinoma which, according to him, arises from the metaplasia of the endometrium above cervical obstruction. This may produce either an epidermoid carcinoma, or in association with adenocarcinoma, produce the picture of an adenoacanthoma. Eden and Lockyer[2] have pointed out that most of the squamous celled cancers of the body are associated with chronic endometritis resulting in cell metaplasia of the columnar epithelium into stratified squamous epithelium. They, however, make a brief mention that a few cases of primary squamous celled carcinoma have also been described in the body of the uterus when epithelial pearls and the general appearance described in connection with the same type of growth in the cervix are present. Meyer[6], however, explains epidermization from basal cells residual beneath the epithelium from the time of fœtal and early childhood development. Kaufmann[4], discussing the metaplasia of epithelium, regards the replacement of cylindrical epithelium of the uterus in chronic endometritis by layers of squamous epithelium which may cornify, as only a rare possibility. He with Hunziker[3] believes that the existence of 'heterotropic islands of squamous epithelial cells' is a result of developmental variations, and opines that these may be the starting point of primary solid epidermoid carcinoma. He further points out that primary squamous celled carcinoma is a rare entity. In our files this is the only case of solid epidermoid carcinoma of the corpus and, as such, we think it of value to report.

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* From the Department of Pathology, Agra Medical College, Agra, U. P., India.

CASE REPORT

A Hindu female aged 50 years was admitted in the Thomason Hospital because of prolapse of the uterus for one year and bleeding per vagina since five months. She had menopause 8 years back and the last child was born 16 years back. Local examination revealed complete prolapse of the uterus with cystocele and rectocele. Clinical diagnosis: Adenocarcinoma of the fundus with prolapse of the uterus.

The uterus with its appendages was removed.

PATHOLOGICAL EXAMINATION

Gross: Specimen consisted of uterus, cervix, both fallopian tubes, and both ovaries. Cervix was 3x2x1.5 cm. in dimensions. The external surface showed marks of adhesions except round the external os where whitish grey mucous surface was present for 0.5 to 1 cm. from the external os. The cervical canal was patent and 0.5 cm in diameter. The mucosa was raised into longitudinal folds and was whitish grey in colour. There was no area of ulceration or congestion. Uterus was 7x7x3cm. in dimensions. Its external surface was smooth, but at places marks of adhesions were present. It was red in colour in most of the area. The myometrium varied from 0.75 to 1.5 cm. in thickness. Endometrium could not be identified as the cavity was full of friable greyish mass of tissue which was attached on all sides to the myometrium. This mass of tissue started 1 cm. above the internal os. Consistency was soft and elastic with nodular feeling of the tissue in the cavity of the uterus. Fallopian tubes on both sides were 8 cm. long and varied from 0.5 to 0.75 cm. in diameter. The lumen of both was patent. The external surface was smooth and the mucosa did not show any abnormality. Ovaries were 3x1.5x0.5cm. each. The external surface was smooth and yellowish in colour. Consistency was firm and elastic. They were soft to cut, and the cut surface in both the ovaries showed pale yellow mass of tissue.

Microscopically, the tumor was a typical epidermoid carcinoma with a fair degree of squamous and keratinised differentiation and formation of pearls of keratinised cells. To exclude the possibility of such a cancer having spread from the cervix upwards, serial sections at a distance of 3 mm. were cut from the external os to the fundus of the uterus. The first appearance of the tumor was found in a section taken through the body of the uterus 1 cm. above the internal os. This definitely proved that the tumor primarily arose in the body of the uterus.

Diagnosis: Primary epidermoid carcinoma of the body of the uterus, grade II.

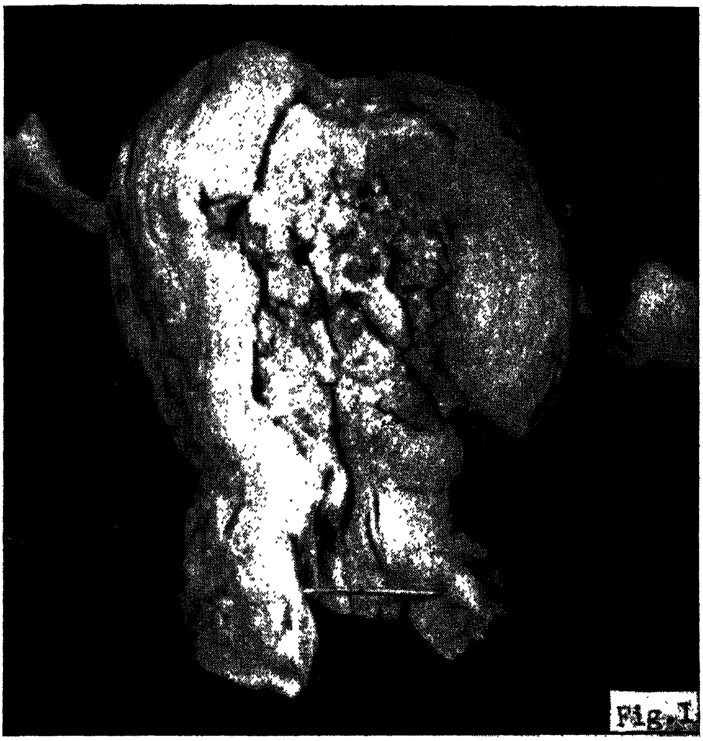

Fig.1 Uterus opened to show the gross appearance of the epidermoid carcinoma of the body.

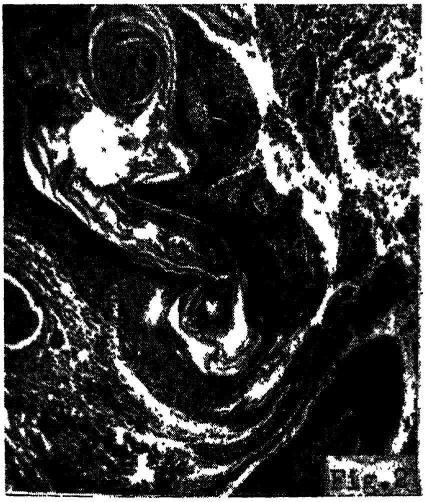

Fig. 2. Microscopic appearance of the tumor showing a fair degree of squamous and keratinised differentiation and formation of pearls. Hematoxylin and eosin stain. x 430.

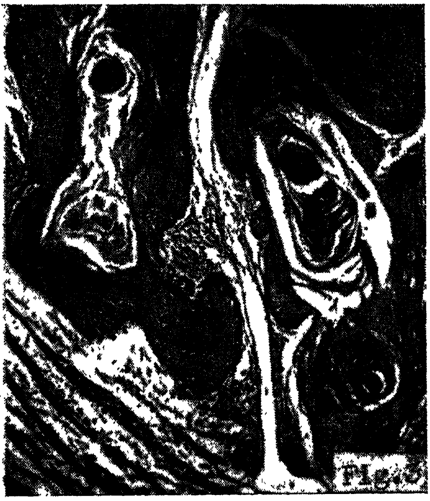

Fig. 3. Another view of the same tumor showing extensive keratinisation and cornification. No glandular arrangement can be seen. Hematoxylin and eosin stain. x 430.

COMMENTS

This case is interesting because it does not conform to the usual types of squamous cell carcinoma of the corpus uteri. There is no stratification and cornification of the surface or acinar epithelium as is found in adenoacanthoma. Most of the cases included under the epidermoid carcinoma are those which are preceded by squamous metaplasia usually following cervical obstruction resulting from irritation by retained menstrual flow and debris. The microscopy in such cases reveals masses of cells resembling squamous epithelium intermingled with glandular carcinoma. There is also some evidence of chronic endometritis. In the case reported, there was no associated glandular carcinoma, but only solid infiltrating masses and pearls of squamous epithelium of the type seen in cervical cancers. Kaufman[4] has reported the occurrence of double carcinoma—a carcinoma springing from the glands, adenocarcinoma, and the malignant proliferation of the metaplastic surface epithelium, squamous cell carcinoma. This is called, by most of the writers as adenoacanthoma. A pure epidermoid carcinoma as the one described, without an associated glandular carcinoma or acinar metaplasia, has thus not been commonly recognised, though the possibility of such a tumor has been accepted by various writers[3],[4],[6]. We feel that a primary solid carcinoma of the corpus, of the type seen in the cervix, can only arise from fœtal inclusions of squamous epithelium in the corpus epithelium as a developmental variation, and that such tumors do not represent malignant transformation of the metaplastic endometrium, but are genuine epidermoid carcinomas. This view is in keeping with the views of Meyer[4], Hunziker[3], and Khanolkar[5].

SUMMARY

A case of primary solid epidermoid carcinoma of the body of the uterus has been described.

The usual cases of squamous celled carcinoma reported in the literature are really cases of adenoacanthoma where the acanthomatous appearance is due to malignant transformation of the metaplastic surface or acinar epithelium.

The pure epidermoid carcinoma is considered to be arising from fœtal squamous epithelium rests, as a result of developmental inclusion, and is very rare.

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A FILARIAL SURVEY OF PALACOLE TOWN

P. Somasundaram *

1. INTRODUCTION

Palacole is a municipal town in the deltaic taluka of Narsapur in the West Godavari district of the Madras Presidency. It is situated about 12 miles inland from the sea (*vide* Map). It has an area of about 2 sq. miles with a population of 19,829 as per 1941 census. The town is divided into 12 wards, and has a total of 4332 assessed buildings.

The township is situated in a water-logged area, there being more of water than of land surface. It is surrounded by a number of main and subsidiary irrigation canals. The main irrigation canal, Nidadavole Narsapur canal, (photograph No. 1) runs also through the town, separating wards 1, 2 and a part of 3 from the rest of the town.

There are extensive rice fields all round the town. The canal water is used for irrigation of these fields throughout the year, except in the months of May and June. The town abounds in gardens; cocoanut, plantain and orange groves abound everywhere. Palacole forms an important trading centre for these fruits.

A huge weekly fair is held on Saturdays, which attracts a congregation of about 60,000 to 70,000 people drawn from the neighbouring areas. Business worth nearly 2 lakhs of rupees is said to be transacted every week. People gather from places mainly from within the district, Narsapur, Bhimavaram, Tanuku, Maruteru, Penugonda, Achanta, etc., and also from the adjoining districts of East Godavari, Kistna, Vizagapatam (North and South) and Guntur.

Though the people are rich, they use a minimum of clothing, both during day and night, probably because the place is hot and moist. Very few use mosquito nets.

All types of houses, from the modern concrete type to mud huts, could be seen in this town. Except in very few houses, there is considerable amount of overcrowding.

There is one Government dispensary with an Assistant Surgeon as the Chief Medical Officer. A fair number of private practitioners have established themselves in the town. Among these are a few followers of the

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Indian system of medicine. The medical aid available in the town may be deemed adequate.

Filarial surveys of the town had been undertaken in 1945 and 1947 to ascertain the extent of prevalence of filariasis, and to suggest suitable preventive measures.

Palacole is connected by rail, road and canal. Train, bus and boat services establish fairly good communication with the external world.

2. *Water supply and drainage*

Palacole has a protected water supply since 1928, derived from the irrigation canals. Water flows in these canals throughout the year except during the months of May and June when the canal is closed for repairs.

The town is peculiar in having 83 large fresh water tanks, each 100 x 100 yards on an average, in and around it. Of these, 13 are in a ruined condition and the remaining 70 are used for watering gardens. Most of them are covered with aquatic vegetation, mainly water hyacynth, lotus and *Pistia stratiotes*. The majority of these tanks are private owned and are situated in gardens. Before the introduction of protected water supply, these tanks served as sources of drinking water and for domestic purposes. The water of the tanks is now used for irrigating gardens. There are quite a large number of private wells besides public wells, the water in all being slightly brackish.

Drainage:—The country is generally flat, without any pucca drainage system for the town. The town has 9,451 yards of kutcha drains, and 7692 yards of masonry drains.

The sullage water is drained partly into tanks and into branches of the irrigation canals, and partly on to the road margins. At a number of public water taps, stagnant pools have formed close to or a little distance away from the taps, due to the inadequate drainage of waste water.

3. *Soil*

Black alluvial soil constitutes the surface layer. The subsoil water level is variable from place to place, about 6 to 12 ft. from the ground level.

4. *Meteorological conditions*

Rainfall:—Vide table 1. The annual rainfall in 1947–48 works upto 47″.12. The South-West monsoon is the prevailing one. Observations of maximum and minimum temperatures and relative humidity were made during the period of this survey in July 1948. These are tabulated and appended at the end. The average maximum and minimum temperatures worked out as 82°.F and 79.°F respectively during the survey. The relative humidity ranged between 68 per cent. and 92 per cent. The total rain fall during the second half of July 1948 was 11.41″.

5. *Vital statistics* :—Vide table 2. The birth rate works up to 40.5 and the death rate to 21.0 for the year 1947. There is practically no large swing in these rates from the average Presidency rates. The infant mortality rate is about the same as that in any other town.

6. *Hospital Statistics* :—Vide table 3. The figures relating to elephantiasis and filariasis from 1939 to 1947 are furnished. The average annual rate for these diseases works out to 0.06 per cent. and 0.6 per cent. respectively, of the total admissions for all diseases.

7. *Malaria* :—Malaria is practically negligible in this town, as indicated by the history as well as field investigation. Of 168 children examined at various places in the town, no enlargement of spleen could be detected. From the history gathered from the local doctors it is noticed that there occur only few stray cases of malaria in the town.

8. *Filariasis* : *History of the Disease* :—Available evidence gathered from elderly people showing signs of filariasis, indicates that the disease has been in existence in this town since several years, *i.e.*, 50 or more. From enquiries it was gathered that several places in the West Godavari district, mainly Narsapur, Bhimavaram, Maruteru, Achanta, Veeravasaram etc., are endemic for filariasis. The ancient history of the disease in this locality is by no means clear.

There is a popular belief among the people of Palacole that in spite of the closing down of all the cesspools in the locality in 1928 there was noticed no appreciable abatement either of filariasis or of mosquitoes in the town. Oiling of other water collections too, they maintained, was not productive of any reduction in the mosquito population. This incidentally cast doubt whether *C. fatigans* was the only or even the prime vector in this locality.

9. *Methods and Technique* :—The present survey covered a period of 20 days from 10-7-48 to 30-7-48. The survey was conducted systematically, ward by ward. A temporary laboratory was set up in the local choultry. In each ward the inmates of about 25 per cent. of the occupied houses were interrogated or examined, and the existence of any of the known manifestations of the disease was recorded. The disease was classified and recorded under the following headings :—

(a) Lymphangitis.

(b) Elephantiasis sub-divided into

1. Leg
2. Arm and
3. Genitalia.

(c) Enlargement of glands.

(d) Chyluria.

This enquiry and clinical investigation covered a population of 5,957 individuals taken from all wards and representing all ages, which is a fair cross section of the inhabitants of the place. Several difficulties had to be confronted but were partly got over during the survey. Examination of women folk was not possible. Even men did not readily submit themselves to a detailed clinical examination, particularly when the genitals happened to be the seat of trouble. Table 4 gives certain details of the survey. The population surveyed was classified under males and females in most of the wards. It was not possible to make a similar classification in wards 2, 6, 9, and 10. In the other eight wards, where it was possible to classify under sexes, the proportion of males and females was nearly equal. Similar proportion was expected to prevail in the four wards mentioned above where the classification under sexes was not done. In all, 5,957 people were seen. A clinical examination of all the people could not be done and reliance had to be placed in some cases on their own statements. Practically all the people who declined to be examined gave a negative history. Out of 5,957 persons contacted for survey, 474 persons of both sexes (7.95 per cent.) showed obvious signs of filariasis and gave history of previous attacks. The incidence of the disease, judging from this survey, is slightly greater in the female (250 cases—8 per cent. of the total female population examined) than in the male (224 persons—7.5 per cent. of the total males examined). Photos Nos. 2, 3, 4, 5 and 6 show cases of elephantiasis.

Of the 474 cases, 363, or 76.6 per cent. were elephantiasis of the leg. Of these, 134 (37 per cent.) were males and 229 (63 per cent.) females. The occurrence is thus far greater among the females than among the males. Out of the 474 cases of filariasis, 88 (18.6 per cent.) were cases of elephantoid scrotum. Elephantiasis of the arm constituted 3 per cent. *i.e.*, 14 out of 474 cases, and 3 per cent. gave history of attacks of lymphangitis. And enlargement of the glands of the groin of filarial origin was present in 3 per cent. Only one case with history of chyluria was obtained.

The figures obtained for lymphangitis and enlargement of glands were low. This, no doubt, was due to imperfect clinical examination and their actual incidence must be several times more.

During the survey, two cases of acute filarial condition were observed, which showed also symptoms of gastro-enteritis, such as vomiting, frequent watery motions, abdominal pain and fever. The night blood was positive for microfilaria in both these cases. Probably these manifestations were filarial in origin.

10. *Age Distribution* :—Vide graph and Table 5. The lowest age group in which the incidence of disease was noticed was 10–15. From this group it shows a steady increase until the maximum incidence is reached in the age group 36 to 40. Thereafter there was a fairly steep decline.

11. *Distribution Of The Disease In Various Wards* :—The prevalence of filariasis was found to be less extensive in wards 1, 3, 4 and 7, and more in the other wards of the town. With this proviso, the disease may be said to be prevalent more or less uniformly in the town. It has been observed during the survey that generally labourers did not show much tendency to elephantiasis. On the other hand, it was common among people who lived in affluence, for example the Vysia community, and led a sedentary life. Some unexplained cause may be operative in bringing about this disparity.

12. *Night Blood For Microfilarial Examination* :—Night blood was taken at random in different localities of each ward. Mostly, it was taken from those who showed no visible signs of the disease. From each ward night blood was obtained from about 50 people. The blood was taken between the hours of 9 p.m., and 10-30 p.m., from people of varying ages and living under different conditions and in different localities in the same ward. Only a single thick smear was taken from each individual. The slides were stained in a 50 per cent. dilution of J. S. B., stain No. 1. They were subsequently decolorised and stained with hematoxylin to obtain better details. More night blood samples could not be taken owing to lack of sufficient co-operation from the public. Out of 556 slides examined, 83 (14.9 per cent.) were positive for microfilaria. Positive cases were observed in every ward without exception and with almost uniform frequency.

Special attention was paid to the study of the microfilarial type. The graceful curves of the larvæ in the smears were noteworthy. The cephalic space measured was much less than double the width of the larvæ. The nuclei were quite well-stained and prominent, enabling easy enumeration. The nuclear column did not extend to the tip of the tail, nor did the last two nuclei show any enlargement. All these pointed to the type being *W. bancrofti.*

The reservoirs of infection are almost equally distributed throughout Palacole. Practically in very street there was at least one case showing microfilaria in the night blood. These act as the source, and in the presence of a dense insect vector propulation the vicious circle goes on.

13. *Entomological Survey—Mosquitoes:*—Larvæ :—A thorough search was made to discover the breeding places of mosquitoes. The following situations were searched :—

1. Fresh water tanks—private and public. 2. Kutcha drains. 3. Stagnant pools near public water taps. 4. Stagnant waters by the side of branches of the irrigation canal. 5. Others—household breeding places.

The fresh water tanks, both private and public, were generally covered extensively with aquatic plants, *viz.*, water hyacynth, *Pistia stratiotes*, chara, duck weed, lotus, etc.

Most of the tanks were so thickly covered with these vegetations as even to completely obscure the water surface in some cases. Tanks, both private and public, were examined for larvæ for nearly 10 days, but none could be detected on making the usual laddle dips. And it was very nearly decided that there was no breeding in the tanks. The aquatic vegetation was then examined one by one in detail. When *Pistia stratiotes* was suddenly taken out and put in a glass of water, several larvæ and also pupæ were seen sticking on to the roots by their syphon tubes or trumpets. These larvæ were found to belong to the subgenus *Mansonioides* and were subsequently confirmed by identification after breeding out. The larvæ have short syphon tubes with a black shining horny tip. They thrust their syphon tubes into the roots of the plant and apparently obtain thus their requirement of air. They seldom come to the water surface. If undisturbed, they were seen never to come to the surface even for several hours. Similarly, the pupæ were seen sticking on to the roots by their trumpets. Following this observation, all the tanks were resurveyed. Wherever this plant (*Pistia stratiotes*) was present, breeding was found to be profuse. In some instances as many as 60 to 70 larvæ were seen to stick on to a plant. Heavy breeding has been observed even in places where the growth of this plant was so thick as to obscure the water surface completely. Most of the tanks contained this plant, floating with hanging roots, and without exception larvæ were seen sticking to their roots. Thus, very heavy concealed breeding was disclosed to be taking place associated with this plant.

Careful scrutiny did not reveal any breeding associated with other types of aquatic plants. However, a constant watch has to be kept to see whether breeding will recur associated with other vegetation, specially water hyacynth, when once the *Pistia* is removed. This, by the way, will be an observation of absorbing interest. Photographs of *Pistia stratiotes* and of a few tanks which contained this plant are added hereto.

Adult Mosquitoes :—1826 adult mosquitoes were captured from the several wards of the town during the period covered by the survey. Anophelines to Culicines were in the ratio of 48.3 to 51.7. Thus, they were approximately in equal proportion. The following species were identified:—

Anophelines.	*Culicines.*
A. subpictus.	*Mansonioides.*
A. vagus.	
A. annularis.	
A. culicifacies.	*Culex fatigans.*
A. hyrcanus.	

The man-hour-catch (Culicine plus Anopheline) ranged from 3 to 60. The density of the Culicine mosquito was high in wards No. 5, 11 and 9. Out of 1826 mosquitoes, 51.7 per cent. were Culicines. The man-hour-catch of the Culicines ranged from 3.6 to 60. Among the Culicines, mosquitoes belonging to the subgenus *Mansonioides* formed 78.1 per cent. The mosquitoes were dissected and infection searched for in the thorax and the proboscis with the results shown in the sub-joined table. Limited experiments were also conducted regarding the biting propensity of *Mansonioides*. Precipitation test was employed, using anti-human serum and serum from the blood content of the mosquito's stomach. Out of 19 specimens tested, a positive precipitin test was obtained in 15, giving a percentage of 79. This shows that *Mansonioides*, at least in this locality, exhibits a far greater anthropophyllic than zoophyllic tendency.

TABLE 6.

Mosquitoes.	No. dissected.	Positive for infection.			
		Thorax.	Proboscis.	Total	Percentage
Anophelines :					
A. subpictus. ..	185	..	..	..	..
Culicines :					
Mansonioides. ..	250	30	1	31	12.4
C. fatigans. ..	48	1	..	1	2.1
Others. ..	24	..	..	..	..
Total ..	322	31	1	32	10.0

Out of 322 Culicines dissected, 10 per cent. were positive for infection Of the infected mosquitoes, 97 per cent. belonged to the subgenus *Mansonioides* and 3 per cent. to *Culex fatigans*. Only one case of proboscis infection was noticed, and that was in *Mansonioides*. In 185 *A. subpictus* dissected, no infection was encountered.

From the above findings, it is concluded that *Mansonioides* are the chief vector species for filariasis in the town, and *C. fatigans* plays but a minor role in the spread of the infection. In the light of this, the popular observation referred to above, *viz* that closure of cesspools and oiling operations of tanks did not produce any diminution in the filarial or mosquito incidence, appears to have some scientific basis, most likely accounted for by the subaquatic habits of the *Mansonioides* larvæ. Nor is it surprising that the oiling prophylaxis proved ineffective. No literature has so far come my way incriminating *Mansonioides* as the vector of filariasis in this Presidency.

From a merely preventive aspect no further survey is necessary, as sufficient material has been adduced to prove the high filarial endemicity of the place. Further survey, however, may be interesting from the academic aspect.

14 *Summary* :—(1) The Palacole Municipal town is an endemic filarial place. The rate of prevalence of infection is 22.8 per cent. This percentage includes both the clinical manifestation rate and the microfilarial rate.

(2) *Mansonioides* appears to be the chief vector and breeds in tanks in association with *Pistia stratiotis*. *Culex fatigans* plays only a minor role.

(3) The peculiarity in the mode of breeding of *Mansonioides* is emphasised.

(4) *Microfilaria* have been demonstrated in the night blood of a high percentage of people investigated. Evidence is in favour of these being of the *bancrofti* type.

I am deeply grateful to Rao Bahadur Dr. K. M. Mathew, Director of Public Health, Madras, for affording the necessary facilities for conducting the survey. My thanks are due to Dr. N. G. Pandalai, Professor of Bacteriology, Andhra Medical College, Vizagapatam, for the liberal supply of anti-human serum prepared in his laboratory, and for his helpful suggestions. My thanks are also due to the staff of my organisation, particularly Dr. L. Chandrasekhara Rao, and to the Municipal Health Officer, Palacole, and his staff for the valuable services rendered by them during the survey.

TABLE 1.

Statement showing the meteorological data recorded in Palacole town.

Date.	Maximum.	Minimum.	Dry bulb.	Wet bulb.	Relative humidity.	Rain fall in inches.	Rain fall during 1947-1948.		
16-7-48	.82 °F.	82 °F.	Readings not taken.			..	1947	July	12.34"
17-7-48	,82 ,,	80 ,,	80 °F.	72 °F.	68%	..	,,	Aug.	5.45"
18-7-48	.85 ,,	78 ,,	80 ,,	76 ,,	83%	0.45	,,	Sept.	9.35"
19-7-48	.80 ,,	76 ,,	75 ,,	72 ,,	81%	0.96	,,	Oct.	3.18"
20-7-48	.82 ,,	78 ,,	76 ,,	73 ,,	87%	1.33	,,	Nov.	4.63"
21-7-48	.85 ,,	80 ,,	80 ,,	74 ,,	75%	0.10	,,	Dec.	5.88"
22-7-48	.84 ,,	82 ,,	80 ,,	76 ,,	83%	0.22	1948	Jan.	0.0"
23-7-48	.84 ,,	78 ,,	80 ,,	77 ,,	87%	0.45	,,	Feb.	0.85"
24-7-48	.82 ,,	78 ,,	78 ,,	75 ,,	87%	3.15	,,	Mar.	0.0"
25-7-48	.82 ,,	78 ,,	76 ,,	74 ,,	91%	1.50	,,	Apr.	0.0"
27-7-48	.84 ,,	80 ,,	78 ,,	76 ,,	92%	0.45	,,	May	0.35"
27-7-48	.82 ,,	78 ,,	78 ,,	76 ,,	84%	1,30	,,	June	5.09
28-7-48	.82 ,,	78 ,,	77 ,,	74 ,,	87%	1.30	,,	July	..
29-7-48	.84 ,,	80 ,,	78 ,,	74 ,,	83%	..		Total	47.12
30-7-48	..	..	82 ,,	78 ,,	83%	0.20		Annual rainfall	47".12
Average	.82.8	79.0			Total.	11".41			

TABLE 2.

Vital Statistics, Palacote Town.

Months.	1946		1947		1948			
	Births.	Deaths.	Births,	Deaths.	Birth.	Rate.	Death	Rate.
1. January	43	53	58	41	48	29.1	35	21.1
2. February	30	28	53	21	43	25.8	38	22.9
3. March ..	35	31	64	31	46	27.7	42	25.9
4. April ..	70	33	43	32	73	44.0	23	13.9
5. May ..	40	28	56	27	66	39.9	45	27.1
6. June ..	45	40	64	38	50	30.1	51	30.8
7. July ..	56	55	93	35	..	..	..	..
8. August	60	41	94	52	..	..	..	..
9. September	56	48	96	53	..	..	..	..
10. October	61	42	75	33	..	..	..	..
11. November	46	25	85	27	..	..	..	..
12. December	63	31	74	28	..	..	..	..
Total ..	605	455	855	418	..	..	..	..
Rates ..	30.5	20.3	40.5	21.0	..	..	..	..

TABLE 3.

Government Dispensary, Palacole

	1939			1940			1941			1942		
	Filaria.	Elephantiasis.	Total admissions.	Filaria.	Elephantiasis.	Total admissions.	Filaria.	Elephantiasis.	Total admissions.	Filaria.	Elephantiasis.	Total admissions.
Total for the year.	325	12	28320	96	12	36782	455	13	37888	602	21	34733
Percentage to total admissions.	1.1	0.04	..	0.26	0.03	..	1.2	0.03	..	1.7	0.06	..

	1943			1944			1945			1946			1947		
	Filaria.	Elephantiasis.	Total admissions.	Filaria.	Elephantiasis.	Total admissions.	Filaria.	Elephantiasis.	Total admissions.	Filaria.	Elephantiasis.	Total admissions.	Filaria.	Elephantiasis.	Total admissions.
Total for the year.	66	33	27106	76	9	24056	39	40	18303	53	15	19670	89	..	22404
Percentage to total admissions.	0.24	0.12	..	0.31	0.03	..	0.21	0.21	..	0.26	0.07	..	0.39	Nil	..

TABLE 4.

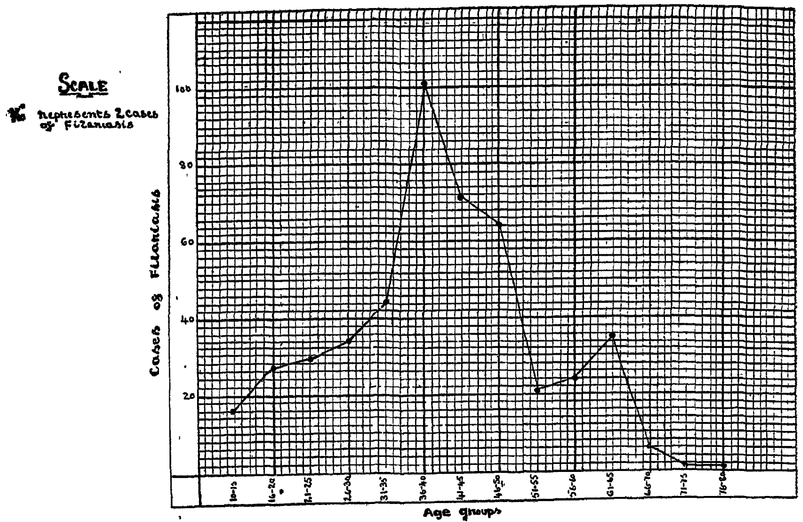
WARD	Total examined or Interrogated.			Total filarial and Elephantiasis cases seen.			Filariasis.								Blood examination (night blood)	
							Elephantiasis.					Lymphangitis	Glandular enlargement.	Others.	Total Examined.	No. with mirofilaria.
							Leg.			Arm	Genitals.					
	M	F	Total.	M	F	Total.	M	F	Total.							
I	126	92	218	5	15	20	3	14	17	..	1	..	2	..	14	3
II	..	..	737	34	11	45	14	9	23	1	19	..	4	..	51	5
III	132	126	258	3	3	6	2	3	5	..	1	..	..	..	56	4
IV	168	159	327	6	3	9	3	3	6	..	4	..	..	..	61	5
V	102	83	185	28	27	55	16	22	38	1	6	10	..	1	39	6
VI	..	..	1041	31	31	62	22	28	50	2	14	..	1	..	54	10
VII	94	107	201	8	10	18	6	9	15	1	1	..	2	..	44	9
VIII	151	138	289	25	33	58	11	30	41	1	11	4	2	..	36	8
IX	..	..	958	24	28	52	14	28	42	1	11	..	..	..	32	3
X	..	..	842	16	18	34	10	14	24	4	8	..	..	..	56	18
XI	207	222	429	20	36	56	15	36	51	..	5	..	..	..	52	8
XII	244	228	472	24	35	59	18	33	51	3	7	..	3	..	61	4
Total	..	..	5957	224	250	474	134	229	363	14	88	14	14	1	556	83
																14.9%

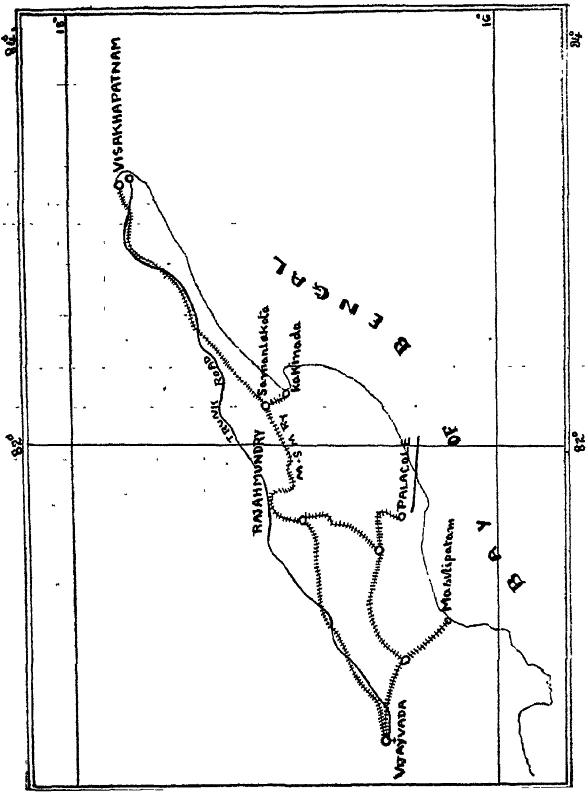
TABLE 5.

Ages	10–15	16–20	21–25	26–30	31–35	36–40	41–45	46–50
	16	27	29	34	44	101	71	64
Percentage	3.4	5.7	6.1	7.1	9.3	21.3	14.9	13.5

Ages	51–55	56–60	61–65	66–70	71–75	76–80	Total
	21	24	35	6	1	1	474
Percentage	4.4	5.1	7.4	1.3	0.2	0.2	

Graph showing Visible manifestation of Filariasis in different age groups in PALACOLE





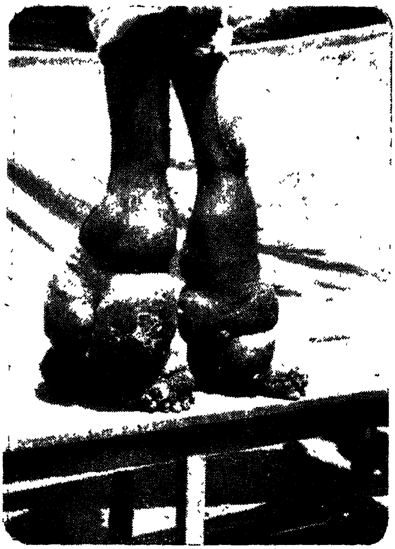
No. 1

Nidavole-Narasapur Canal

No. 3

No. 2

No. 4



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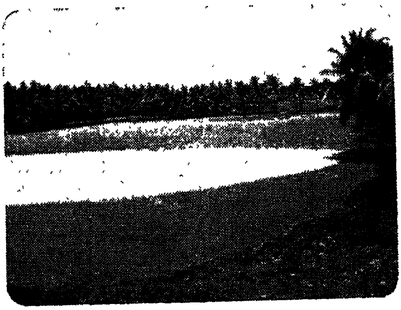

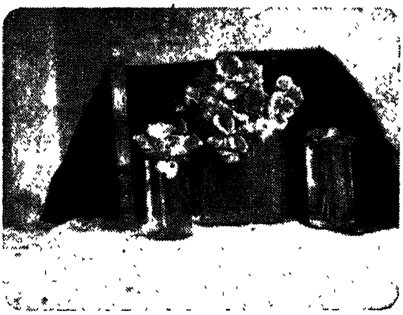

Pistia stratiotes

AUREOMYCIN

A Review of Its Present Status*

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INTRODUCTION

Aureomycin is an antibiotic derived from a strain of Streptomyces aureofaciens. It was discovered by B. M. Duggar[11] while working at the Lederle Laboratories Division of the American Cyanamid Company. He introduced the drug to the medical profession at a conference of the New York Academy of Science on 21st July, 1948. The specific name "aureofaciens", signifying a golden appearance, has been given for *two* reasons![11] (1) At a certain stage in the growth of the colony of this fungus, or of a smear (an amalgamation of colonies), there is "typically" the production of a golden yellow pigment in the moist or hygrophorus substrate mycelium. (2) The antibiotic too, is faintly golden yellow. A—377 is the other name for Aureomycin. Aureomycin has an unusual degree of potency and range of activity, acting against many Gram positive and negative organisms [5], [13]. However, the most outstanding feature of aureomycin is the striking spectrum of activity exhibited by this latest amongst the antibiotics against many Rickettsiae, and certain viruses.[1,10,23,26,31]

PHYSICAL PROPERTIES

Aureomycin is available as a yellow crystalline hydrochloride salt which is soluble in distilled water but somewhat less soluble in isotonic sodium chloride solution. These solutions are acid (pH 4.5)[5]. Aureomycin is soluble in acid and alkaline solution but is almost insoluble at pH 7.[14]

Stability: The activity of this antibiotic deteriorates rapidly in alkaline solutions at room temperature.[13] At pH 2.5, the substance is stable but at pH 8.5, 25°C, it loses—

12% of its activity in 30 min.
20% of its ,, in 1 hour
and 40% of its ,, in 2 hours[14]

Aureomycin kept in dry powder form in sealed ampules or in capsules retains its potency for at least seven months at room temperature.[13] Solutions kept frozen at—20°C retain their activity for long periods.

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*Literature upto the end March 1949 has been reviewed.

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Concentrated solutions (2 mg per c.c.) in distilled water have retained their activity for over two weeks at 4°C and also at 37°C. The potency of aureomycin solutions in blood agar, saline, plasma or broth deteriorates rather rapidly.[13]

ABSORPTION

After oral administration, aureomycin is rapidly absorbed through the gastro-intestinal tract.[13] The oral route of administration is preferred, because the drug is promptly absorbed and the results are uniformly consistent.

BLOOD CONCENTRATION

A qualitative assay is difficult, but quite low levels like 0.3-2.5 mg/cc have been detected in the blood serum.[9] The plasma levels, after oral doses of upto 1g given six hourly, have usually been found to be about 2 micrograms per millilitre or less, but the methods were not satisfactory.[13]

EXCRETION

Aureomycin is very rapidly excreted in the urine and the excretion continues for 2-3 days after a single dose of 0.5-0.75 g.[13,20]. Levels upto 320 mg/cc have been detected after oral administration.[9] The greatest rate of excretion in the urine occurs between 4-8 hours after oral administration. If similar absorption and excretion take place from repeated oral doses, the intervals between such doses should be about 8 hours in order to maintain the maximal absorption and excretion rates.[13]

According to Collins and his co-workers,[6] the antibiotic can be detected in the urine for more than 33-55 hours. Their findings, too, suggest that the optimum interval between oral doses of aureomycin should be about eight hours.

Aureomycin is not detected in bile obtained from the common bile duct during oral administration of the antibiotic, although aureomycin is not inactivated by bile in vitro.[13]

SIDE EFFECTS AND TOXICITY

The toxicity of aureomycin is quite low, except after intravenous administration. As a whole, the drug is well-tolerated and is relatively non-toxic for all practical purposes, when given in therapeutic doses.[26] There are almost no side reactions.[14]

Therapeutic doses upto 60 mg/kg body weight per day, given orally, do not give rise to any toxic reactions, except for occasional nausea and transitory vomiting.[26] The commonest side-effects are anorexia, nausea, vomiting and diarrhoea. All these are transitory features. The onset of vomiting should not prevent one from continuing the treatment. In fact, vomiting is no contra-indication to therapy.[23] It has been observed that nausea and anorexia due to large doses of aureomycin administered for prolonged periods, are usually decidedly alleviated by the use of aluminium hydroxide preparations. Looseness of bowels with bulky stools has been frequently observed by Finland, Collins and Paine. According to these authors true diarrhoea is uncommon.[13] A reduction in the dose of aureomycin or discontinuance of the drug results in prompt cessation of looseness of bowels.[13]

There has been no evidence of renal irritation or impairment of hepatic function. No rashes nor any fever or leucopenia have been observed.[13] However, a rising temperature for a few hours and a shock like picture with a drop of blood-pressure, and tachycardia may be seen with large doses. Some investigators have observed a mild transitory anaemia. Haemoglobinuria has been occasionally observed after massive dosage.[14]

Some patients complain of mild drowsiness. No neurological abnormalities like nystagmus, vertigo, tinnitus or auditory disturbances have been observed.[25] An intra-muscular injection leads to local irritation and variable degrees of pain, from moderate to severe, and lasting from several minutes to several hours.[9] Allergy to aureomycin has not been reported. The patients may however become allergic to aureomycin just as they might become to other antibiotics.

FACTORS INFLUENCING AUREOMYCIN ACTIVITY

Aureomycin is effective only against vigorously multiplying organisms but not against fully grown or resting cultures. Aureomycin is much more effective in an acid than in an alkaline medium—the reverse of streptomycin.

Filtration of solutions of aureomycin in water, broth or urine through Seitz, Mandler or sintered glass filters, does not appreciably reduce the activity of aureomycin.

Resistance: There is no significant tendency for the development of resistance to aureomycin in organisms either in vitro or in vivo.[13,20] This is in sharp contrast to streptomycin. All organisms of the same species, isolated from the same patient, before during or after the treatment with aureomycin, for varying periods upto one month or longer, were equally sensitive to this antibiotic.[13]

EXPERIMENTAL WORK.[5]

In Vitro Studies.

The following organisms are susceptible to aureomycin in the concentration mentioned below:—

		Per millilitre	
1	β- haemolytic streptococcic strains, Group A, D, F and G	0.3–1.25	microgram
2	Diplococcus pneumoniae, Types 1, 11 and 111	0.1-0.3	„
3	Staphylococci	0.6	„
4	Some strains of B. Coli aerogenes	5.0	„
5	Klebsiella pneumoniae	1.0–5.0	„
6	H. influenzae	2.0	„
7	Brucella suis and abortus.[26]	0.75	„

Pseudomonas aeruginosa and strains of Proteus are not inhibited even in high concentrations.

The antibiotic appears to be bacteriostatic rather than bactericidal except in high drug concentration[5a]. The human serum seems to have an inhibitory effect on the antibiotic's activity[5a] and to obtain an inhibitory concentration in the presence of 50% serum, about 50 times the concentration is necessary as compared with that in broth.

In Vivo Studies.[5]

Harned, working on dogs, showed that in therapeutic doses, aureomycin rapidly passes the blood-brain barrier,[14] and two hours after an intravenous injection, substantial amounts (40 microgram/cc) remain in the blood stream. Bryer and his co-workers[5] found that the serum level after an intramuscular injection in rabbits is 20 mg/Kg, and dogs is 40 mg/Kg.

1.5 mg/cc of serum was found in from 15-60 min. after the injection. Significant blood levels did not appear after one hour.

The dogs receiving 20 mg aureomycin per Kg. body weight twice daily, regularly had 0.3-1.25 micrograms of aureomycin per cc in the serum, in samples drawn one hour after the injection.

Rats, rabbits and dogs have been found to tolerate very large single doses. *e.g.* 3-3.5 g/Kg. body weight in a single day.[5] The lethal dose$_{50}$ (LD$_{50}$) on intravenous injection in mice, is between 50-100 mg/Kg body weight; on subcutaneous injection, it is 3000-4000 mg/Kg body weight.[5] Thus, animal experiments show that the significant blood levels are present only one to two hours after administration, the time varying with the dose and the route employed.[5]

In man, Dowling and his co-workers detected that after an intramuscular injection of 100 mg. aureomycin to adults, the peak concentration in blood was reached at about the third hour. Detectable concentrations were present at the 12th hour.[10]

According to Wright and his co-workers, however, the highest blood levels occurred two hours after oral administration of 300 mg. aureomycin *viz.* 2 micrograms per cc.[33]

If 700 mg. aureomycin are given orally, the peak concentration in the serum occurs about the 6th hour, and all sera show detectable amounts at 12th hour.

Orally given to a man weighing 150 lbs. in doses of 500 mg. twice a day and 40 mg. intramuscularly at six hour intervals, the blood levels of 0.6-2.4 micrograms per cc of serum are observed one hour after an injection.

High concentrations like 40-80 micrograms per cc are observed in urine which is coloured greenish yellow. The antibiotic is not detected in the cerebro-spinal fluid.

In man, the coli-aerogenes and streptococcus faecalis infections of the urinary tract, Rocky mountain fever (Eastern type), and Brucellosis respond dramatically when the antibiotic is given in a dosage of 10-60 mg. per Kg body weight per day, orally in 6-8 divided doses.

There is no evidence of cross-resistance with penicillin, streptomycin, polymyxin or bacitricin, in any of the organisms tested. On a weight basis, aureomycin is less effective than penicillin against most of the coccic organisms, but is about as effective as streptomycin against most of the Gram negative bacilli[13]. The greatest advantages of aureomycin are its wide range of activity, effectiveness of oral therapy and low toxicity.

INDICATIONS FOR USE

The precise indications for the use of aureomycin are not yet fully established, except in certain diseases. However, aureomycin acts against:

1. Rickettsial Infections.
2. Primary atypical pneumonia (Infection of unknown origin).
3. Virus diseases like lymphogranuloma venereum and psittacosis
4. Bacterial Infections.
   - A Many gram positive and negative organisms.
   - B Acute Brucellosis.
   - C Tularaemia.
   - D Sulphonamide, penicillin and streptomycin resistant organisms. (aureomycin can be effectively used in patients sensitive to any of the above drugs).
   - E Coli-Aerogenes group of infections—of the urinary tract and peritoneum.
5. Ocular infections: i Bacterial, ii Viral.

In the following, aureomycin has been found useful, but its value has not been clearly defined as yet:—

Bacterial infections caused by

1. Salmonella organisms. The drug may be effective in large doses.
2. Gram positive cocci other than those that are penicillin resistant.

The value of aureomycin here is not precisely determined, but its usefulness is anticipated.

Aureomycin is ineffective in Proteus vulgaris and Pseudomonas aeruginosa infections.

Aureomycin has failed to show any therapeutic activity against the following viral infections:

> β strain of influenza, canine distemper, rabies, Newcastle disease, Venezuelar equine encephalomyelitis. &
> M E F—1 strain of poliomyelitis.[31]

Dosage in general:

1. For severe infections like Rickettsial infections and Q fever:— 50-100 mg per Kg body weight per day given orally in divided doses. 300-500 mg per Kg per day have been given in typhoid fever and other salmonella infections without untoward results.

2. For moderate infections like primary atypical pneumonia and most other infections:—

25-50 mg per Kg body weight per day, orally, in divided doses. This dosage should be continued for 5-14 days as judged by the clinical response. Usually, it is given every four hours for the first 24 hours and then six hourly. If definite therapeutic effects occur, the dosage can be reduced to a lower range within a few days.

CLINICAL TRIALS

1. Rickettsial Infections:

The anti-rickettsial activity of aureomycin is now well-established: [1,10,22,23,26,31]. In fact, aureomycin perhaps exerts its greatest influence in this group of diseases.

At first, highly successful animal experiments were reported by Anigstein[1]. In these experiments, a very high rate of survival was seen in guinea pigs infected with a highly virulent strain of Rocky mountain-spotted fever rickettsiæ and the Breinl strain of epidemic typhus.

Following on this, Wong and Cox[31] reported that the drug was highly effective against rickettsiæ of spotted fever, typhus fever, scrub typhus and the Q fever in the chick embryo, *i. e.* aureomycin is a specific for the entire group of typhus rickettsiæ[23].

Rocky mountain spotted fever (Eastern Type):—

The drug is uniformly successful in bringing about a complete cure of this condition.[1,7,10,22,23,26] Ross and his co-workers[23] successfully treated 13 cases of Rocky mountain spotted fever with aureomycin. They found that the temperature came down to normal within 2-1/3 days on an average. Striking clinical improvement was obtained in all cases. Besides the clinical examination, their diagnostic means were the Weil-felix reaction and the complement fixation test. In the two cases reported in detail by them, an embedded tick was removed 9-10 days before admission.

Their dosage schedule was:—

Initial loading doses: 2.5 mg/Kg 1 hourly for 3 doses.

Then 2.5 mg/Kg 2 hourly till temperature is normal for 48 hours.

Then 2.5 mg/Kg 4 hourly.

The mean period of treatment was 6 days.

They also compared the results with those obtained with the Para-amino Benzoic acid (PABA) and found that aureomycin is a more effective agent,[22] and this for several reasons:

With aureomycin:

1 Temperature response is much more dramatic.
   Rapid defervescence occurs 2-1/3 days after initiation of therapy - still shorter time with larger dosage.
   (6-10 days with PABA)
2 Uniformly good results are obtained—whatever be the day of disease when aureomycin is started. (PABA gives good results provided it is given earlier than 7th day of disease)
3 Rash disappears earlier (4 days)
4 Convalescence and average stay in hospital is shorter.
5 Leucopenia and depression of liver function are not seen as with PABA- This was proved by a series of laboratory tests.

Similar dramatic recoveries have been reported by Anigstein et al[1], Schoenbach, Bryer and Long[26], Dowling et al[10] and C. Cooke.[7] Schoenbach, Bryer and Long[26] treated cases on 3rd and 5th day of the disease, and the oral therapy made the patients afebrile in 12-72 hours.[26] Cooke's dosage was 1 g six hourly for 48 hours and then 0.5 g six hourly for 24 hours. (Total = 10g)

Recently, Schoenbach[24] has reported prompt recovery in a case of Brill's disease—recrudescent epidemic typhus—by oral administration of aureomycin given in a dosage of 200 mg one hourly for 3 hours and then 200 mg. 2 hourly day and night for 4 days.[24]

Ross[22] could not determine the optimal dose for this disease. He, however believes that a daily dose of 30-60 mg/Kg, given orally, should give excellent clinical response.[23]

The rapid defervescence is accompanied by such a striking clinical improvement, and the course of the disease is so promptly altered, that usually no supportive treatment is required.

Q fever : This is an acute infectious rickettsial disease due to C. burnettii. Wong and Cox[31] found that aureomycin was effective against Q fever in animals. Lennette found similar results in human beings.[19] Average dose was 2-5 g/day.

Rickettsial Pox : Animal experimental work by Wong and Cox[31] indicates that this new disease will yield to aureomycin.

2 Primary atypical non-bacterial pneumonia :

All pneumonias of known viral, rickettsial or bacterial origin are excluded.

Despite the indeterminate causation of this disease, aureomycin is a valuable chemotherapeutic agent.[25] Schoenbach and Bryer have reported gratifying results in 13 cases.[18] A rapid defervescence and a decided clinical improvement occurs when patients are treated with aureomycin. The laboratory diagnostic criteria used by these investigators were the development of agglutinins from streptococcus MG and the cold haemagglutinins.

Their dosage schedule was:

30-50 mg/Kg. per day. It was given as initial loading dose :

	100-250	mg. every hour for 3 hours
Then	,,	mg. 2 hourly till patient becomes afebrile.
Then	,,	mg. 4-6 hourly for 2-5 days.

Temperature comes down to normal within 24 hours in the majority of cases, the range being 12-72 hours.

Subjective clinical improvement coincides with the lysis of temperature. Cough, however, improves gradually. Weakness of varying degree was evident during convalescence. Most of the cases were previously treated with sulfonamides and penicillin but with no response.

3 Virus diseases :—

Lymphogranuloma venereum :

Following a clue that aureomycin was highly effective in the treatment of mice infected intracerebrally with the virus of lymphogranuloma venereum,[31] Wright and his co-workers decided to try out this drug in human cases.[33]

As is well-known, as yet there is no specific treatment available for this disease. The various sulfonamides, penicillin, stibophen, and antimony-potassium tartrate, at best, only remove the secondary infection.[34] These investigators gave 20 mg daily by intramuscular infection. Within four days, the gland was reduced in size and the rectal bleeding stopped. Inclusion bodies also disappeared rapidly (within 48 hours) and proctitis showed a marked improvement. Even the stricture often softened down, and stool diameter may be doubled. It is believed that the antibiotic effect of aureomycin is not limited to a single strain.[33] Chronic cases may require an additional surgical approach. Collins, Paine and Finland[6] have reported cases of bilateral lymphogranuloma inguinale that progressed favourably on aureomycin therapy.

Wright[33] treated three cases of granuloma inguinale with aureomycin with eminently satisfactory results.

Psittacosis: Animal experiments by Wrong and Cox have shown the remarkable therapeutic activity of aureomycin against the entire group of psittacosis-lymphogranuloma viruses.[31]

4 Bacterial Infections:

A. Various Gram positive and negative organisms.[13]

Pneumococcic pneumonia: This responds rapidly within 18-36 hours to aureomycin.[13] The results are comparable to those obtained with penicillin and the sulfonamides, the advantage of its use being that the pain of the penicillin injection, and the toxic reactions of the sulfonamides, are obviated.

Meningococcaemia too responds to aureomycin.[13]

Aureomycin is also indicated in scarlet fever and the allied streptococcal infections and in subacute bacterial endocarditis resistant to penicillin.

Gonococcal urethritis responds very well to aureomycin.[13] It is felt however that the results are distinctly inferior to those obtained by a single dose of 300,000 units of penicillin in beeswax-peanut oil. All the same, aureomycin would still be useful in case of penicillin resistant gonococci, and also when the patient refuses an injection and wants an oral remedy. Aureomycin in doses larger than 1.5 g. per day, for 2 days, would give results practically identical with those obtained with penicillin.

Good results of a permanent nature are infrequent in cases of chronic infectious of urinary tract. Temporary relief however results in most of the cases.[13]

Non-specific urethritis responds well to aureomycin[13]; successful treatment of E. coli infections of the urinary tract is also reported.[5],[26]

Typhoid fever:

Two cases of typhoid fever were treated with aureomycin with favourable initial responses by Bryer and his co-workers in Sept. 1948[5]. Four patients with typhoid fever showed no clinical or bacteriological response when treated with aureomycin.[10] Three early cases of typhoid fever treated with aureomycin in daily dosage of 60-100 mg/Kg per day by mouth, and 3-5 mg/Kg per day parenterally, have resulted in negative blood and stool cultures within 48-72 hours. Clinical response has varied however, with defervescence occurring in 24 hours, 8 days & 11 days respectively.[26] In November 1948, Finland, Collins and Paine reported that most Gram-ve bacilli, including typhoid and other salmonella organisms, are inhibited by 25 micrograms of aureomycin per ml. or less.[13] They treated 5 cases. The results were good in one, doubtful in two and failed in two. The findings are thus equivocal. However, it is felt that some benefit is obtained, since soon after aureomycin therapy, blood, stool and urine cultures become negative.

Large doses may however be required.

Similar equivocal results are obtained in the treatment of the typhoid carrier state. The organisms are again passed into the stool as soon as the drug is withdrawn. Probably this is because the drug does not act in bile in the gall bladder.[13] In some cases of salmonella infectious of the gut, favourable results have been reported.[13]

B *Brucellosis :*

In December 1948, Eisele and McCullough showed that combined streptomycin and sulfadiazine is a specific for Br. abortus infections.[12] Stimulated by this research, Spink and his co-workers thought of trying out this combined treatment in the more malignant form of this disease, *viz.*, the brucella melitensis infection. The clinical results were, however, not satisfactory. Also, there was the vestibular dysfunction due to streptomycin, as also other obvious disadvantages like prolonged period of hospitalisation.[30]

In the meantime, Shaffer had already demonstrated the antibrucella activity of aureomycin,[27] and Bryer and his co-workers treated one case of brucellosis with favourable initial response in September 1948.[5] After a little experimental study, Spink and others switched over to aureomycin. And the most unexpected thing happened. The clinical results far surpassed the expectations, and the relatively small oral doses of aureomycin altered the clinical course of the disease in the most dramatic way.[30] These investigators already had a large experience in the treatment of brucellosis by vaccines, sulphonamides and streptomycin with or without the sulphonamides. A consistent and an abrupt change in the clinical course of the disease was observed only in patients receiving aureomycin. In most of the cases, the temperature became normal in 2-3 days.

Their dosage schedule was:

1st day 0.1 g.
2nd day 0.6 g.
3rd day 1.6 g.
4th day 2.0 g. Then 2.0 g. daily till 11 days in divided doses.

The advantage is that aureomycin can be given to an ambulatory patient, as an outpatient remedy, and hospitalisation is unnecessary. The immediate results have been striking but a long follow-up is needed to evaluate the drug fully. After a long follow-up, the authors advise 4-6 g daily for 2 weeks to prevent any bacteriological relapse, instead of the dose as tried above. Schoenbach too has reported clinical cures.[24]

C. *Tularæmia :*

In 1947, Woodward et al observed that para-amino-benzoic acid exerted a slightly beneficial effect in mice experimentally infected with Bact. tularensis[32]. The highly specific role of streptomycin in the treatment of tularæmia is well-known[2,3,15,16,17,18].

The rabbit fever perhaps affords streptomycin its clearest and most favourable indication for use. But the undesirable side-effects of streptomycin are obvious.

It was found in March 1948 that chloromycetin increased the survival time in *animals* experimentally infected with Bact. tularensis.[28]

In March 1949, however, Woodward and his co-workers found that aureomycin exerts significantly beneficial effects in experimentally infected mice. Chloromycetin, in vivo, has been shown to be much less effective than aureomycin or streptomycin; and since aureomycin does not produce toxic complications, and can be given either orally or intramuscularly with equally good results, a thorough, comparative, clinical trial of the 3 antibiotics in tularaemia is indicated.

Woodward et al cured 3 cases of tularæmia by oral aureomycin, given in dosages of about 0.5 g 4 hourly, the total dosage varying from 15-32 g[32].

D. Many organisms resistant to sulphonamides, penicillin or streptomycin succumb to aureomycin. Moreover, they do not develop resistance to aureomycin[13].

E. Bryer et al successfully treated two cases of E. coli infection of the urinary tract[5].

5 Ocular Infections [4]:

Aureomycin acts as an efficient local antibiotic in

i	Staphylococcal conjunctivitis :	Treatment is advised for at least two days to prevent recurrence.
ii	Influenzal conjunctivitis	A cure occurs within 24 hours.
iii	Pneumococcal ,,	
iv	Inclusion ,,	
v	Epidemic kerato-conjunctivitis :	Treatment must be started early within four days of onset.
vi	Dendritic keratitis :	Rapid healing of cornea occurs.

Aureomycin appears to be effective in Mooren's ulcer, and may be of some value in vernal conjunctivitis. It is probable that the improvement is due to the antibiotic action on secondary infection.

It is anticipated that aureomycin will be an effective remedy for trachoma.

Combined local and oral therapy is preferred in Diplococcus (Morax-Axenfeld) ulcers, Friedlander's bacillus ulcers, and in general whenever there is a severe infection.

Ocular infections in which aureomycin probably is of no value are :

Erythema multiforme
    —conjunctivitis
    —keratitis
Ocular pemphigus
Perinand's conjunctivitis
    —leptotrichos
Sympathetic ophthalmia
Vernal conjunctivitis,
Molluscum contagiosum,
Streptothrix concretions.

Mode of use : A 0.5-1.0% solution of aureomycin borate in isotonic saline is commonly used. It has a pH of 7.5-7.8 and is only mildly irritating to the normal eye and entirely non-irritating to the inflamed eye.

The borate salt in powder form is stable but is unstable in solution, though it retains most of its activity when kept at +4°C. In solution and at room temperature, the activity of the drug disappears in about 24 hours. Hence, frequent use of the drug over a short period of time is perhaps the best method of use.

Dosage : Make a solution : 1cc—5 mg aureomycin

1-2 drops every 2 hours till clinical response.

With less frequent instillation, many cases respond in 48 hours.

Conclusion:

Discovered in the wake of penicillin and streptomycin; this new antibiotic—aureomycin—gives promise of being one of the most versatile antibiotic drugs yet discovered. However, further extended trials in many a different disease are required. The usefulness of the drug should be evaluated in different forms of tuberculosis, more especially because the soil dilution cultures of S. aureofaciens are known to inhibit M-tuberculosis.

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SOME ASPECTS OF TYPHOID FEVER.*

R. V. Sathe †

In spite of the widespread prevalence of the enteric group of fevers, throughout this country, there are very few statistical records of the disease, so common in Bombay and in all the large towns in India[5]. The town of Bombay has had a very heavy incidence of typhoid during the last decade, and the disease may now be said to be endemic in this place. Cases occur throughout the year, with exacerbations at one or other part of the year. The town forms a suitable source for observation of this disease; and the admissions to any medical institution in this place would offer a representative picture of the disease. With this aim, I have reviewed the records of 220 cases treated at the Bhatia General Hospital between the periods January 1946 to April 1949.

Diagnosis.

The clinical diagnosis of all these cases has been typhoid fever; most of the cases have run a very characteristic course. With some of them there has been another case or two in the family. However, for an accurate diagnosis, one of the following criteria should be satisfied :

i) The blood culture should be positive, or

ii) The Widal agglutination test should be positive with a significant agglutinin titre, or

iii) The bacilli be isolated from the urine, or

iv) From the stools of the patients.

The Widal test was positive in 100 cases. In 53 it was done but not found positive. In the 67 remaining cases it could not be done owing to difficulties in the institution. It is felt that if the blood cultures, urine cultures and stool cultures were done, a large number of the cases would have yielded positive findings. In spite of this feeling, however, the following observations are made on the 100 cases only, which have shown a positive Widal agglutination reaction.

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* Paper read before the Maharashtra and Karnatak Provincial Medical Conference at Kolhapur in August 1948.

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INCIDENCE

Sex.

Of the 100 cases, 66 were males and 34 females.

TABLE NO. 1.

Age Incidence

Age in years	No. of cases
1 to 10	12
11 to 20	32
21 to 30	39
31 to 40	8
41 to 50	4
50 to 60	5
Total ..	100

Lowest age.............1 1/2 years

Highest age.............57 years.

Age.

The above has been the distribution of the cases according to age groups; the youngest case being in a child 1½ years old and the oldest in a man aged 57. Typhoid is a disease of the adolescent, and is uncommon in the young and the old. This group shows maximum incidence in the second and third decades, which include 71 of the cases.

Occupation.

As to occupational factors, the patients have come from all classes of workers from clerks in offices, mill-hands, teachers, house workers and so on. It is not the occupation that has been the cause of their disease but general sanitary conditions in the town, as a result of which all are exposed to the same common risks.

Season.

It has been felt that the incidence is higher in the hot months of summer and in October. The following is the analysis of the cases, month by month, in the corresponding years. The cases are, therefore, almost evenly distributed, throughout the year.

TABLE No. 2.

Year	1946	1947	1948	Total for 1946-47-48.	1949
Jan.	1	..	5	6	2
Feb.	..	..	1	1	4
March	..	1	1	2	11
April	1	2	4	7	1
May	3	2	2	7	..
June	...	5	2	7	..
July	2	1	5	8	..
Aug.	5	..	4	9	..
Sept.	4	4	6	14	..
Oct.	4	3	3	10	..
Nov.	..	4	2	6	..
Dec.	1	1	3	5	..
	21	23	38	82	18=100

SYMPTOMS

Fever.

Of the symptoms at onset, the one single symptom of importance has been the fever. It has been low, moderate or high at onset, the onset being gradual or abrupt. Headache was present in a large majority of the cases. It was excruciating and troublesome and was localised to the frontal or vertical areas, of the head. One feature about the headache was that it was always most marked at the onset of fever and tended to wear off, so that by the end of the first week it had practically disappeared. If it persisted thereafter, a mistake in diagnosis was likely, or else an intracranial complication should be suspected. Body pains were present in a large number. They were, however, always milder than the headaches. An initial diarrhoea occurred in a few cases and vomiting suggestive of a gastritis occurred in still fewer cases. Respiratory symptoms were uncommon at onset, but in a few cases nasal catarrh followed by cough, characterised the onset of fever. These cases resembled influenza or a respiratory infection in the beginning.

The temperature charts of these patients have been very illuminating. In a few cases, the temperatures were highest at onset and after a variable course settled down to normal. In other cases, it rose gradually in a ladder-like fashion. Some cases showed typical intermittent temperature throughout the course, simulating septic temperatures or malaria. In a few again, the chart was very irregular. Reviewing all the charts, one sees that the classical text-book description of a ladder-like rise during a week, a continued fever in second week and a gradual fall in a stepped fashion in third week, did not hold true in these cases and was present only occasionally. The height of temperature at the onset was no guide to the severity of the disease, and in some cases with very high temperatures at onset, the fever subsided within 14 days, with a very moderate degree of severity in the clinical picture. On the other hand, cases with a typical gradual onset with a ladder-like rising chart in the early stages, went through a prolonged course with many complications. An abrupt rise in an otherwise uniform chart was an ominous occurrence. It indicated possibility of hyper-pyrexia; in others it indicated severe toxæmia and, in a few, perforation. An abrupt fall in temperature suggests either a crisis or else an internal hæmorrhage, peripheral failure, or collapse. A falling temperature without clinical improvement is always an ominous combination. The longest duration of fever in the above cases has been 57 days, and the shortest 10 days.

Rigors

Rigors were present in many cases in this series. They occurred in a few cases at their onset; they were then indicative of the severity of the onset. But in others, they occured during the course. In some they recurred daily like malarial rigors, in some they occurred even two or three times a day. Blood investigations were done to rule out malaria; in others, therapeutic quinine administration failed to check the rigors. Some of the cases, with frequent rigors succumbed. But rigors were not necessarily of serious import. It has been suggested that they are due to showers of emboli of organisms from the bowels into the portal canals of the liver.

Sweating

Sweating occurred in a very large number of cases; it has been profuse and frightening in some cases; it occurred in all cases with rigors; it was present with peripheral failure. In spite of it, however, the temperature persisted.

TABLE No. 3.

Details of Toxæmia in 20 cases.

	No. of cases	Expired.
Toxæmia alone	14	7
Toxæmia with delirium	3	3
Txæmia with unconsciousness ..	3	Nil
	20	10

Toxæmia

Toxæmia was present in varying degrees in 20 of the cases. In the 14 milder cases it lead to mental dulling, followed by apathy and stupor. Coma occurred in 3 cases. Subsultus was associated with these cases. In 3 others insomnia and delirium resulted. Some of these toxæmic cases showed rigidity of the neck and limbs with a positive Kernig's sign. The height of temperature, the toxæmia, the rigidity and the aspect of the patient suggested meningeal involvement. In only one of these cases lumbar puncture was done, and the C. S., fluid findings in this case were normal. It is our rule not to perform a lumbar puncture in these cases unless it is indicated by some more definite signs, *e. g.*, cranial nerve palsies. Otherwise, as a rule, in typhoid, these findings are due to meningism and not meningitis. Of these 20 cases with toxæmia 10 died; of the 3 patients with delirium, all 3 died, while the 3 cases with coma, all recovered. Toxæmia, therefore, should induce one to a guarded prognosis ; delirium in these cases makes the prognosis much worse.

Nervous System

Of the nervous manifestations, one case developed a hemiplegia and died. Psychosis was noted in another case. The mental changes in typhoid recover almost invariably, though sometimes after a prolonged course of some months. It is suggested that this loss of cerebral function is due to the fixation of the toxins in the brain cells, without producing cell death.

Respiratory System

Respiratory complications were present in 29 cases, hypostatic congestion and broncho-pneumonia were the most common. Some cases showed only a bronchitis—this occurred in the early stages.

Cardio-vascular System

The commonest manifestation was the slow pulse in the first week, which became typically dicrotic by the end of the first week; later on, however, tachycardia ensued with disappearance of dicrotism.

Myocarditis was evidenced by the soft first mitral sound, in many cases accompanied by a soft systolic murmur.

Peripheral circulatory failure occurred in 10 cases. It was characterized by rapid, small pulse; cold clammy, sweats; fall in blood pressure; rapid shallow respirations; pallor or cyanosis, and an asthenic look about the facies. The condition is due to a toxic vaso-dilatation of the peripheral vessels, and the treatment of this condition is always a difficult problem. Adrenalin 1 in 100,000 1 c.c. intravenously, 6 hourly; pitressin ¼ to ½ c. c. subcutaneously 4 hourly; ephedrine hydrochlor gr. ½, 6 hourly, are given to raise peripheral pressure. Coramine 1 c.c. 6 hourly, or caffeine sodii benzoas grs. vi 6 hourly have been recommended as cardiac stimulants. Saline and recently, plasma transfusions have been given to raise the volume of circulating fluid. Percorten (Ciba) has been recommended for its blood pressure raising and antitoxic effects; but, with all these, the treatment of this complication is entirely unsatisfactory and recovery is rare. All the 10 cases in this series which developed peripheral failure expired.

Gastro-intestinal System

Of the Gastro-Intestinal manifestations two are very common and very troublesome—distension and diarrhœa.

Distension is at times due to improper feeding, in which case, it is readily corrected by revising the diet. Milk, glucose and fruit juices and carbohydrates are the offending factors, and need omission from diet. More often, however, the distension is due to toxæmia. It leads to marked discomfort; at times, it embarrasses the heart in a weak patient. Hæmorrhage and perforation are more likely to occur in cases with distension. In the 9 cases where distension occurred, there was not a single instance of hæmorrhage; perforation was suspected in 1 case but on operation none was found; round worms in distended bowels were found; this patient died. The remaining 8 recovered. Adjustment in the diet, turpentine stupes and enema, carbachol or prostigmine were the remedies used, and were effective.

Diarrhoea occurred in 20 cases, during the course of the fever. The maximum number of stools in a day was 9. It responded to treatment in 15 cases. But in 5 cases it tended to be protracted and persistent.

In the treatment of this complication, the following routine was followed: On the commencement of diarrhœa, the patients were put on D. D. (diarrhœa diet) which consisted of 2 feeds of tea or coffee with 2 teaspoonfuls of milk only; 2 feeds of thin rice conjee, 2 feeds of arrowroot conjee and 2 feeds of apple or pomegranate juice. Milk and glucose were omitted completely. At times and in severe cases, patients were given saline water or plain water for 24 hours, and diarrhœa diet later. Kaopectate drachms 2 to 4, three to four times a day, Bismuth Carb drachm one after every motion, and opium in form of Tr. opii or Dover's Powder were given. Starch and opium enema was used when necessary. In spite of this rigorous treatment, some patients never came under control. One felt as if cases of diarrhœa could be grouped in two classes: i) those that responded to dietetic adjustments, without or with additions of drugs, almost immediately or with a little patience. ii) Cases that did not respond to any form of therapy, no matter how thorough one may have been in its details. In these latter cases, hœmorrhage and perforation are to be dreaded. Or the patient may succumb to extreme malnutrition with general exhaustion. In this group of 20 cases hœmorrhage or perforation did not occur. But 5 cases proved to be persistent, and 4 of these died of peripheral failure. The 5th death was post-operative. Table No. 4 shows some details of these cases with diarrhœa.

TABLE NO. 4.

Diarrhœa in 20 cases. Details;

Maximum No. of stools per day	7	6	5	8	2	6	5	4	4	5	9	4	5	5	5	5	6	6	4	5
Day on which diarrhœa started	16	24	13	6	16	14	15	38	11	16	15	30	8	14	12	15	11	5	7	7
Duration in days	8	5	4	9	2	10	8	3	8	3	9	4	6	3	7	15	14	5	3	3
Results ..	c	c	c	c	c	c	EP	c	c	c	P	c	c	c	c	E. Pf.	P	P	c	c

C: Checked
E: Expired

P: Peripheral failure
Pf: Perforation.

Hæmorrhage occurred in 3 cases. It was mild or moderate in 2 and profuse in 1. This case expired.

Perforation occurred in 3 cases, and all of these cases died. In a 4th case, perforation was suspected and the patient operated upon. At the operation, however, no perforation was found, the intestines were distended with gas, and round worms were detected in the bowels. This patient died after operation.

Other Symptoms

Parotitis occurred in a few cases; bed sores occurred in a few also, but no accurate data regarding both these are available.

Of the urinary complications, the commonest was retention of urine. In a number of cases it was postural and, therefore, only functional. It yielded to proper psychological approach and assurance to the patient. In the rest, it was due to general weakness or toxœmia. Carbachol and prostigmine helped a majority of these. Only four cases needed the use of the catheter. In these cases, risks of infection were certainly involved. But, with Sulpha or penicillin therapy, such complications were overcome.

Otitis media occurred in one case only. Rose spots were not recorded in any case.

TABLE No 5.

Details of Relapse.

One Relapse in 16 cases; Two relapses in 2 cases.

After how many days ..	15. 4. 3. 6. 16. 15. 9 16. 8. 3. 6. 3. 6. 8. 14. 5. 7. 8.
Imputed to ..	.. .. R .. R. .. R. .. .. R .. ..
Duration of relapse in days ..	12. 16. 3. 6. 17. 4. 23. 10. 20. 7 13 17 22 10 8 3 8
Result	c c c c E c c c c E c c c c c c c c

c: Cured
E: Expired.
R: Addition of Rice To Diet.

Relapses

Relapse occurred in 16 cases, in 2 of which, there was a 2nd relapse. In 4 of these cases, the relapse commenced just after addition of soft rice to the diet, but in the remaining 12, there was no ascribable cause, the diet, rest and all other details of treatment having remained unchanged. There is a tendency on the part of the medical professional to ascribe the relapses to additions to the diet or to movements (*e. g.* sitting up in bed). In view of the above findings, such presumptions do not seem to be justifiable. Table No. 5 gives some details regarding these relapses, which should be of interest.

TABLE No. 6

Age	Duration of disease in days
17	24
10	49
24	62
11	37
10	23
15	68
8	23
28	17
45	26
19	30
7	23
30	23
21	19
19	16
10	19
18	8
21	31
45	18
45	16
16	68
24	44

MORTALITY

Death occurred in 21 cases; the ages of patients who died, with the duration of disesase before death are shown above.

TABLE No. 7

Death in 21 cases in decenniums.

Age Group	Number of deaths
1 to 10	5
11 tc 20	7
21 to 30	6
40 to 50	3
Lowest age	7
Highest age	45

In decenniums, the deaths have occurred, as above:

If these figures are compared with the incidence of cases in the respective decenniums, it will be seen that the mortality is highest in the fifth and first decades. The disease, though common between 11 to 30 years of age, is more fatal in the very young and the very old.

TABLE No. 8

Causes of death in 21 cases,

Perforation	3
Peripheral failure	10
Hæmorrhage	1
Round worm querry perforation-Expired after operation	1
Toxæmia	6

The causes of death have been tabled above:

LABORATORY INVESTIGATIONS.

A Widal reaction, positive in significant titres of the agglutinins was a requisite for the diagnosis of typhoid in these cases. Blood, urine and stool cultures were not done. Repeated observations of the Widal reaction were not done, as it was not the object in view. The test was repeated a second time in five cases only; a negative reaction turned positive in 2 of these cases; a positive reaction turned negative in one, and in 2 cases, the reaction remained positive but yielded higher aggultinin titres. 5 cases were S. Paratyphoid A infections and of these 3 died. Of the 17 other cases in which S. Paratyphoid A infection was associated with S. Typhoid or S. Paratyphoid B infections, 5 died. Comparing these figures with the 13 deaths in the remaining 78 cases, it appears that the mortality in S. Paratyphoid A infections is very high. No conclusions can be drawn regarding the mildness or severity of the clinical disease, from the agglutinin titres of the Widal reaction. Cases with a positive reaction in lower titres may be mild or severe; so also would cases with higher agglutinin titres.[4]

The blood counts were done as a routine in these cases. Though a moderate leucopenia with rise in mononuclear cells was present in 71 cases, occasionally, varying degrees of leucocytosis were observed even in absence of any complications. The highest white blood cell count recorded is 21000 cells per mm and the lowest 2100.

The urine showed albumin in traces in 44 cases and in larger amounts in another 16 cases. Febrile albuminuria is, therefore, present in over 60% of the cases. In one case mild nephritic changes were observed.

DIET TREATMENT

In the treatment of this condition, I wish to refer to the dietetic treatment. Upto very recently, I used to put my patients on bland liquid diets very rigidly. After the temperature was normal, and the appetite had increased, quantities of some of the dietary articles were increased, without any qualitative changes. After a period of 10 days, soft solids were added, once on the first day, then twice on the second day; then the quality of the soft solid was doubled; then further additions were done gradually. If a rise in temperature occurred, there was a halt in this process; if temperature persisted, dietetic changes were held responsible for the same. Latterly, there is a change in these views. If a febrile patient is suspected to be typhoid and if he is taking food, I now put him on soft solids like rice, soft bread and boiled eggs, unless distension or diarrhœa occurs. At times, when pyrexia is prolonged and nutrition of the body poor, I add solid food to a previously liquid diet, gradually. In a number of cases this is well tolerated, and leads to rapid improvement in the patient's condition. In those patients who have been on liquid diet throughout the febrile course, addition of solid foods to the diet are made on the 3rd or 4th day of normal temperature. By so doing, the nutrition of the patients is maintained, their resistance to infection is strengthened, the frequency of complications is lesser, and the period of convalescence is curtailed.

CHEMOTHERAPHY.

With the advent of the newer chemotherapeutic drugs each one has been tried and credited with a special effect on S. typhoid infections. The sulpha group was the first of these. In the present series, these drugs were given to 18 patients in moderate doses; no particular benefit was noticed.

Florey had prophesied that penicillin in large doses would successfully attack Bact. typhosum. Evans (1946)[3] was of opinion that penicillin exerted a retarding effect on the growth of B. typhosum *in vitro* and *in vivo*. Since then, a number of workers have claimed good results with penicillin.[1] It was used in 29 cases of this series. It was used especially for pulmonary complications. These generally cleared with penicillin, but the typhoid fever took its usual course. In the absence of complications, therefore, penicillin does not seem to be of any value.

Bigger (1946)[2] claims that penicillin and sulphathiazole together exert a synergic action on B. Typhosum. McSweeney (1946)[7] reports on 5 cases of typhoid treated with 10,000,000 units of penicillin and sulphathiazole 68 tablets in 4 days, with excellent results and Laha[6] reports on five cases of typhoid in children, with encouraging results. Such combinations were used in 8 cases without much benefit.

Recently, streptomycin is claimed to be an antibiotic that is effective in B. typhosum infections. Reimann & Price[8] reported on 5 cases of typhoid treated with streptomycin. The drug was given intravenously, 4 gms. a day, for 3 to 4 days and then the dose was reduced. We used streptomycin alone in 2 cases and combinations of streptomycin and penicillin in 6 more cases. Of these 7 died contrary to reported results.

We are, however, on the eve of a significant advance in the chemotherapy of typhoid fever. The recently prepared chloromycetin is reported to have potency in combating typhoid infections. The drug is on the way to this country and we should soon be able to assess the effects claimed for it.

BLOOD TRANSFUSIONS

Lastly, I must refer to the usefulness of blood transfusions in typhoid fever. The indications for its use are:

i) In intestinal hæmorrhage. If the hæmorrhage is profuse, transfusion is the best remedy we possess. In this case, a pulse rate above 140, a systolic blood pressure reading below 80 mm Hg and a hæmoglobin percentage below 40, are the indications for transfusion. The blood should be given by slow drip; rapid replacement may re-induce an arrested hæmorrhage. The quantity of blood given may be large, say, 400 to 500 c.c. and may be judged by the amount of blood lost. The results are excellent.

ii) In petechial hæmorrhages, subcutaneous hæmorrhagic plaques, and oozings from the gastric and rectal mucosæ. In such cases, repeated small transfusions are desirable.

iii) To combat toxæmia. In such cases again, repeated small transfusions are desirable. The results are often dramatic, and they are due to the presence of immune bodies in the transfused blood. Immuno-transfusions are advised in such cases, but even the blood of healthy donors gives good results.

iv) To terminate a prolonged pyrexia.

I have seen on occasions the temperatures settling down to normal with a single transfusion. In other cases, each transfusion has produced a significant fall in temperature, till in two or three transfusions, the patient has become apyrexial. In these cases, with the fall of temperature, the toxæmia resolves, the mental state of the patient improves, and a normalcy is induced.

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CURRENT MEDICAL LITERATURE:
MEDICINE

"Refined" Liver Extract In Tropical Macrocytic Anaemia.—J. C. Patel and Y. M. Bhende. Blood 4: 259-268, 1949. Table 1, Ref. 17.

The purpose of this paper is to show that 2 or 3 ml. of "refined" liver extract is sufficient to produce an optimum response in "Tropical Macrocytic Anæmia" (T. M. A.) thus indicating a similarity in the deficiency of some factor or factors in the causation of pernicious anæmia and this condition, so far as therapeutic response is concerned. The mode of production of deficiency may not be the same.

45 cases of T.M.A. were treated with "refined" liver extracts. The cases are divided into four groups according to the proprietary preparation used. 32 cases gave an optimum response, 7 suboptimum, and 6 did not respond. Of the 6, one did not remain under observation, one responded subsequently to crude liver extract but the remaining four did not respond even to crude extract. The amount of active principle (original liver) needed to produce satisfactory response is more than that required in pernicious anæmia, but there was no qualitative difference. This work also shows that T.M.A. in India does not differ fundamentally from the nutritional macrocytic anæmia found in the United States or elsewhere. Since larger doses of older types of 'refined' liver extract were necessary to produce optimum response than the newer preparation (Examen NP) the authors infer that a considerable amount of active principle was probably not extracted in the older "refined" extracts. The authors advocate the use of newer "refined" liver extract.

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Serum Potassium Levels in Diabetic Coma. Sinden, R. H., Tullis, and Root. New Eng. Jour. Med. **240**, 502-505, Mar. 1949.

The authors stress the importance of variations in the serum potassium levels during treatment of diabetic coma. Critical alterations in these levels may result in a fatal outcome. The causes of a fall in level from the normal of 5.0 milliequiv. per litre are varied. During acidosis particularly of the diabetic type there is an immediate and increasing loss of potassium in the urine. The excessive administration of glucose, especially with insulin results in a rapid deposition of glycogen in the liver, associated with an intracellular shift of potassium as shown by experimental work. One patient received glucose intravenously and subsequently developed a serum potassium level of 1 milliequiv. per litre, the lowest level recorded in literature.

The mere storage of excess of glycogen has no value in the first few hours of the emergency in diabetic coma. If 200 gm. of glucose be given in the first few hours no more than 10 gm. can be oxidised per hour. The remainder is excreted, deposited as glycogen (thereby producing further reduction of serum potassium) or converted into fatty acids.

Since determinations of potassium levels are not always possible, one should always remember that the sudden development of marked muscular weakness or actual flaccidparalysis may mean hypo-potassæmia. In one or two patients a peculiar fish-mouth facial-expression has been noticed.

At the New England Deaconess Hospital, during the 3 years ending April, 1948, in 91 consecutive cases of diabetic coma treated without glucose, there was not a single death in spite of such complications as pneumonia, cerebro-vascular accidents, heart disease, coronary occlusion and chronic nephritis.

E. J. BORGES.

URETHANE (ETHYL CARBAMATE) THERAPY IN MULTIPLE MYELOMA. J. PHILIP LOGE, AND R. WAYNE RUNDLES. Blood 4: 201-216: 1949, 5 Tables. 3 fig. 32 ref.

4 cases of multiple myeloma, 2 of the rapidly progressive type and 2 of the slowly progressive type were treated with urethane; 4-6 gm. per day, reduced to 2 gms if leucopenia resulted, with a total dosage of 120-240 gms in 8-10 weeks. The patients were under observation for 2 periods varying from seven to thirteen months. All the patients showed striking benefit, relating to all aspects of the disease. The early responses to treatment indicate a selection and beneficial alteration in the fundamental abnormalities. The results being better than any produced by previously available therapeutic agents. The relapses in two cases responded satisfactorily to a further course of urethane therapy.

J. G. PAREKH.

THE LEADING CAUSES OF DEATH AMONG PHYSICIANS. F. G. DICKINSON AND E. L. WELKER. J. A. M. A. 139, 1129-1131, April, 1949.

The authors have analysed 3,167 of the 3,230 reported deaths in the obituary columns of the J. A. M. A. They compared these causes with those worked out for the white male population for the same period. White male population figures were used because of the small percentages of females and non-white persons in the physician population.

Heart disease ranks first and is higher in the physicians group, 42.2 per cent as against an expected 38.9 per cent. Cerebro-vascular diseases accounted for second largest number, 12.3 per cent as against an expected 9.5 per cent. Cancer stood third with 11.0 per cent as against 13.3 per cent expected. Only a small percentage of deaths was attributed to each of the other causes, and the shifts in rank were relatively unimportant, with the exception of nephritis, which actually ranked sixth and was expected to rank fifth, and tuberculosis which was far below the expected percentage (0.8 as against 3.1 per cent expected).

The leading causes in the general male population were, in order: heart, cancer, cerebro-vascular diseases, accidents, nephritis, pneumonia, influenza and tuberculosis. The comparatively low cancer death rate may be due to earlier recognition by the physician. Is the high rate from heart disease due to the traditional unwillingness of the physician to refuse to accept calls at all hours even though the result be loss of sleep and irregularity of meals? Or to emotional strain? Whichever the cause, heart disease is really an occupational hazard of the physician.

E. J. BORGES.

SURGERY

TWO COMMON NON-MALIGNANT CONDITIONS OF THE BREAST: DAVID H. PATEY: B. M. J. 96-99: Jan. 15, 1949.

The author attempts to clarify the position with regard to the vague ill-defined group of diseases of the breast, included in the term chronic mastitis.

He recongises two distinct clinical conditions—cystic disease of the breast, which has definite physical signs, and the "pain syndrome" which is a purely subjective disorder.

Cystic disease may be associated with a solitary or multiple cysts—the former being always aspirable with restoration of the breast to near-normal. The latter condition may or may not be amenable to aspiration, depending on the size of the component cysts. The condition bears a superficial resemblance to carcinoma, though skin dimpling and other signs of infiltration are conspicuous by their absence. Sooner or later, the condition tends to become bilateral.

There is enough clinical evidence to indicate that the condition is not pre-cancerous, and the author quotes the opinion of recognised authorities (Swodgood, Gechicter) in support of this view.

On the other hand the belief that the basic cause may be a hormonal upset rests more squarely upon animal experimentation.

Present trends are towards conservatism in the treatment of this condition and simple aspiration is often curative—though other cysts may develop in one or other breast

The "pain syndrome" may take the form of a mere exaggeration of the normal pre-menstrual engorgement of the breast or the pain may occur between the periods. The condition is characterised by the absence of any physical signs.

There is a definite connection between fear of cancer and this condition.

Less frequently, psycho-sexual upsets are a potent factor in its causation, and the condition may logically belong to the realm of the psychiatrist rather than the surgeon. This condition, as is understandable from its etiology, bears no relation to carcinoma.

A. E. DE SA.

HERPES ZOSTER THERAPY: PAIN RELIEF BY A SIMPLE PROCEDURE: G. F. FASTING: New Orleans Med. & Surg. Jour. 101, 378, 1949.

In the treatment of herpes zoster the main interest appears to be directed toward control of pain. For large areas sedatives do not fill the need. When Xrays are used to the appropriate skin and spinal areas, relief, if obtained, is not likely to appear before a lapse of 24 hours. Small doses of posterior pituitrin in only a small percentage of cases gives dramatic relief.

In this paper the simple procedure of sponging the affected skin area with commercial carbon tetrachloride is described as giving rapid and consistent relief. Commercial carbon tetrachloride is cheaper. It is used in dry cleaning and fire extinguishers. Druggists should be encouraged to stock the commercial grades for external use.

A few cases are described in whom instantaneous relief from pain was effected by sponging the affected part with about one ounce of the drug.

E. J. BORGES.

A NEW OPERATION FOR GASTROPTOSIS. ANTON RAABE, ACTA CHIR. Scand. 98, 40-46, April, 1949.

The author describes his technique and results with a new operation for gastroptosis. The results are good only if indications for the operation are strictly followed. These are: Considerable emaciation, severe constipation, retention and discomfort after meals especially on standing up. In the presence of a pronounced neurosis the operation is not likely to cure the symptoms.

The technique consists in placing thin silk sutures 3 deep ones through the upper edge of the pancreas and the lesser curvature where it is at its lowest. When the threads are tightened and tied the stomach is hoisted like a sail, and fixed in a permanent position. A fourth suture should attach the ligamentum teres, where it leaves the liver, to the lesser curvature half an inch proximal to the pylorus. The bend of the pylorus which is due to the pendulous and extended pre-pyloric part is thus raised and the U-shaped stomach loses this shape.

A total of 74 patients were so treated in the last 18 years. In 66 patients neurosis was absent and all of them have been well pleased with the results. The majority have increased in weight and can eat and enjoy all kinds of food. The other 8 patients had a neurotic background and should not have been operated on, except that the other excellent results tempted the surgeon to try the operation on them.

E. J. BORGES.

THE PREVENTION OF AMPUTATION NEUROMA. STEPHEN TENEFT (ITALY) - Jour. Internat. Coll. Surg. 12, 16-20, 1949.

A painful amputation stump occurs in almost 30 per cent. of cases in the author's experience. Various surgeons have reported incidence which varies between 6 and 72 per cent. The most frequent causes of painful amputation stumps are nervous in origin and here an amputation neuroma is often the cause. The pathologic interpretation of pain is difficult but it appears that through the ends of neurofibrils proliferated in cicatricial connective tissue stimuli can be picked up and are perceived in the brain centre as pain.

Numerous attempts to prevent amputation neuroma have been made, and have usually failed. The author tried to solve the problem by a physiological approach. Connective tissue is not a favourable medium for the proliferation of neurofibrils. Muscle tissue, normally richly supplied with nerve endings may reasonably be considered as representing the most favourable medium. The author experimented on rabbits and found that if the amputated nerve end was placed unsutured between muscle fibres an amputation neuroma did not form. Histological sections of the nerve end, made at various periods after the operation, showed that the neurofibrils proliferated between muscle fibres and finally ended on them without the formation of a neuroma.

This method was tried in six human cases with complete success. In one case who already had a painful thigh stump, the neuroma was resected and the severed stump implanted into a nearby muscle, with complete recovery. The author suggests that this method may be given an extended trial.

E. J. BORGES.

PEDIATRICS

A METHOD OF INCREASING THE LUNG BLOOD SUPPLY IN CYANOTIC CONGENITAL HEART DISEASE. N. R. BARRET AND RAYMOND LALEY—B. M. J. 1: 699-702, 1949.

Anastomosis between the pulmonary and a systemic artery and valvulectomy have been the two methods that have been used so far to increase the blood supply to the lungs in cyanotic congenital heart disease. But sometimes these operations may not be possible and, in others, operations of such magnitude may not be desirable. The authors report six cases in which the parietal pleura from the upper mediastinum, from the dome of the pleura, and from the upper half of the chest was removed. Powdered asbestos was then dusted on to the raw surfaces, the chest closed, and, after instituting temporary drainage, the lung was completely re-expanded. This increased the blood supply to the lungs and then there was improved exercise tolerance, diminution of cyanosis and less frequent cyanosis. There was significant improvement in the arterial oxygen saturation after the operation in three out of four cases.

G. COELHO.

PATHOLOGY

SPECIFIC ESTROGENIC AND ANDROGENIC SMEARS IN RELATION TO THE FOETAL SEX DURING PREGNANCY. H. E. NIEBURGS, AND ROBERT B. GREENBLATT. Am. J. Obst. & Gynec. **57**: 356-363, 1949.

In a study of vaginal smears from 2500 women, the authors observed that an estrogenic activity was indicated by cytolysis of epithelial cells, while the androgenic activity was suggested by the presence of mucoid material with increased cornification of cells. These observations, when applied to the smears in pregnant women during all stages of pregnancy, revealed a co-relation of findings in the smears with the fœtal sex. A male fœtus was associated with a mucoid cornified (androgenic) or glycolytic smear, whereas a cytolytic (œstrogenic) smear was seen in the case of a female fœtus. The characteristic oestrogenic smear reveals an increase in the number of Doderlein bacilli and an almost complete destruction of cellular cytoplasm with intact nucleii. The typical androgenic smear is characterised by cornified cells with abundant mucoid material. The glycolytic smear is very rare and is characterised by extra cellular deposition of glycogen and intracellular glycopenia.

The method is very simple and is best attempted between the 18th and 26th week of pregnancy. Desquamated cells from vaginal epithelium were obtained by insertion of a cotton applicator into the posterior fornix of the vagina. The staining procedure employed was that of Hæmatoxylin and Carmine for the additional evaluation of glycogen.

Out of 86 pregnancies, only 22, showed characteristic smears and the sex of the fœtus was correctly predicted in 87% (14 out of 16). The results indicate that the maternal hormone levels change in accordance with the fœtal sex. The source of the particular increased hormone is probably the fœtus itself, and the cases which either fail to show these characteristic changes or give erroneous findings may be explained by the fact that the maternal hormones probably mask those of the fœtus.

P. N. SHAH.

CARCINOMA CELLS IN SPUTUM AND BRONCHIAL SECRETIONS: A STUDY OF 150 CONSECUTIVE CASES IN WHICH RESULTS WERE POSITIVE. WOOLNER, L. B., AND McDONALD, J. R. Surg. Gynec. & Obstr. **88** : 273, 1949.

The occurrence of grossly visible fragments of neoplastic tissue in the sputum of patients with cancer of the lung has been observed for many years. In this study, the authors have examined sputum or bronchial secretions for carcinoma cells from

1,600 patients. In 150 of these cases results were reported positive and in 1,450 they were considered negative. In 146 out of these 150 cases, the source of the typical cells was believed to be a tumour in the bronchial tree. In 141 out of 146 cases a final diagnosis of primary or metastatic carcinoma of lung was made. In 3 cases diagnosis made on the basis of smears were proved to be false positive. In two cases the final diagnosis whether inflammatory or neoplastic was not definitely established.

The technique employed was based on the original work of Dudgeon and Wringley. Smears of sputum or bronchial secretions from non-neoplastic diseases of lung reveal squamous, and ciliated columnar epithelial cells, macrophages and various inflammatory cells. In general, it may be said, that all the characteristic features of malignant cells seen in tissue sections, with the exception of invasion, can be applied to isolated cells, singly and in clumps, occuring in sputum or bronchial secretions. Carcinoma cells in smear could be distinguished from normal cell by numerous typical characteristics including large size, variation in size and shape of the cells and of the nucleus, the nuclear cytoplasmic ratio, hyperchromatism of the nucleus and presence of large nucleoli. In general cells undergoing mitosis are rarely found in smears of sputum or bronchial secretions and are of no importance in the diagnosis of carcinoma by this technique.

G. V. TALWALKAR.

THE CYTOLOGIC FEATURES OF CARCINOMA AS STUDIED BY DIRECT SMEARS. HAUPTMANN, E.: Am. J. Path. **24**: 1199-1223, 1948.

During the last 20 years the method of diagnosing cancer by visual examination of a single cell or a group of isolated cells, has received more and more attention. In this study the author has examined 188 cases out of which 78 were reported positive and the rest as negative. The smears were made directly from the tumours and were stained by The Wilson and Papanicolaou stain.

Five types could be distinguished among the smears of carcinomas, the squamous cell type, the columnar cell type, the round cell type, the undifferentiated cell type and the oat cell type. The following changes were observed in smears of carcinomas. The size of the cells was in general larger than that in noncancerous processes. The cells were individually disposed or were present in sheets. The cytoplasm of the cells was either scanty or poorly outlined, merging gradually with the background. Few of the carcinomas possessed cells which were relatively rich in cytoplasm. Nucleus was usually larger than that of control group and sometimes attained giant dimensions. Anisonucleosis and poikilonucleosis were almost always present. The chromatin was irregular and was composed of coarse strands and formed a net-like structure. The nucleolus of carcinoma cells assumed very peculiar and sometimes monstrous forms. A larger number of cases must be studied before the validity of other cytologic expressions of carcinoma may be considered as proved.

G. V. TALWALKAR.

ANAESTHESIOLOGY

MYANESIN AS A MUSCLE RELAXANT. HAROLD R. GRIFFTH, M.D., C. R. STEPHEN, M.D., WILLAIM G. CULLER, M.D. AND WESLEY BROWNE, M.D. ANAESTHESIOLOGY **10** : 61—65, 1949

A comparative study of myanesin with curare is made by the authors in both clinical and experimental anesthesiology. Myanesin is a synthetic compound described as O-tolyl ether, one of the substituted ethers of glycerol, a colourless, odourless, crystalline solid. (It is supplied by the British Drug House in the strength of 100 mg. of myanesin in each milliliter: compare with the strength of Squibbs d-tubocurarine (Intocostrin) of 2.7 mg, Abbot's d-tubocurarine 3 mg. and Burroughs & Wellcome's tubarine 10 mg. in each milliliter). The observation of the authors, after a clinical trial of myanesin by using it in the same kind of cases and under the same circumstances as in using curare in 120 cases, is as follows:—

(1) The relaxing effect of myanesin was less predictable in a given case than they had become accustomed to expect with curare.

(2) The duration of relaxation varied, but was not longer than that obtained with a single dose of curare.

(3) Respiratory depression with myanesin was as common as with curare.

(4) There was no evidence to support the contention made by others that myanesin had a sèlective action on abdominal muscles.

(5) Myanesin mixes well with pentothal, but it is not much more effective with barbiturate anæsthesia than is curare.

(6) Generally speaking, the relaxing effect of 10 c. c, of myanesin is equal to that of 3 c. c. of intocostrin.

Administration in conscious patients revealed that the only abnormal neurologic sign was nystagmus with loss of convergence of the pupils, probably from a central effect. Many of the subjects had transient hæmoglobinuria and albuminuria for 24-48 hours after injection and leading to thrombophlebitis in 4 out of 120 cases which is a definite disadvantage as compared with curare.

The authors are of the opinion that myanesin is not a satisfactory substitute for curare in clinical anæsthesia.

B. G. Faria.

BOOK REVIEW

Bacterial and Virus Diseases. By H. J. Parish, M.D., F.R. C., P.C., D.P.H., Pp. 168. Edinburgh: E. S. Livingstone Ltd., 1948.

In his preface the author writes that "this little book has been written to present in convenient form the essential principles of immunology and their practical application in human medicine." The book contains plenty of useful information. It is divided into three parts: general, antisera and serological products for active immunization, and some diagnostic reagents. The chapter headed "historical" gives important dates in the modern development of the subject. With growing emphasis on preventive medicine and specific therapy every practitioner ought to be quite familiar with the various methods now employed in this direction. This book offers this essential information, shorn of the added information found in the larger books. This is a publication that a practitioner should have on his desk.

G. COELHO.

MEDICAL NEWS

COLLEGE OF PHYSICIANS AND SURGEONS OF BOMBAY.

F.C.P.S. EXAMINATION.

The following candidates have been declared to have passed the Fellowship Examination (F.C.P.S.) of the College of Physicians and Surgeons of Bombay held in June 1949:—

NEW REGULATIONS.

OTO-RHINO-LARYNGOLOGY. Desai, Vinay Atmaram. Shah, Kanti Ujamshi.

OLD REGULATIONS.

MEDICINE. Bhatt, Pravinchandra Ramprasad. Damany, Shashikant Jethalal. Master, Thakordas Bhagwandas.

SURGERY. Desai, Naresh Gandabhai. Patel, Maganbhai Shankerbhai. Shroff, Pannalal Dwarkadas.

MIDWIFERY AND GYNAECOLOGY. Deshpande, Meena Madhav, (Mrs.). Kalewar, Vatsala Sambhaji, (Miss). Rane, Vijaykant Atmaram.—Trivedi, Umakant Shamshanker. Wagh, Keshav Venkatrao.

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Examples: 1. Coller, F. A., and Maddock, W. G.: The Function of Peripheral Vasoconstriction, Ann. Surg. **100**: 983-992, 1934.

2. White, J. C., and Smithwick, R. H.: The Autonomic Nervous System, pp. 271, New York, the Macmillan Company, 1941.

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PHYSIOLOGICAL AVAILABILITY OF ESSENTIAL NUTRIENTS
(Nicotinic Acid).

R. G. Chitre* and D. B. Desai*.

Our knowledge regarding the different chemical reactions involved during the process of digestion and utilisation of various nutrients, as well as the special physiological functions these nutrients perform after such transformation, is yet incomplete. This lack of knowledge is one of the fundamental difficulties in the proper assessment of the nutritional potency of a food-stuff. A mere quantitative estimation, chemical or physico-chemical, of a particular nutrient in a food-stuff, would probably lead one to an erroneous conception about its potency, and thus came to be introduced for the first time in the science of nutrition the idea of the physiological availability of different nutrients in a food-stuff *i.e.*, how much of a particular nutrient in a food-stuff is actually utilised by the organism.

When a food-stuff is being digested, the enzymes in the intestinal tract have a limited period for their action on the material during its passage from stomach to colon. During this period, it is likely that the enzymic hydrolysis may not completely set free a particular nutrient, which may pass on to the caecum and colon and be excreted in the faeces under quite a different form during its lower journey, and may not be detected as such even in the fecal residue. That such a possibility exists in case of amino acids has been suggested by Maynard (1). In such cases therefore, the actual availability of the nutrient will be much lower than the quantity estimated by chemical and physico-chemical or even by micro-biological methods, since all these methods have some shortcomings (2).

Recently Elvehjem (3) has rightly stressed this point in his article on "Future Studies in Nutrition". To quote his own words, "The information on the qualitative and quantitative composition of foods is only a starting point, and this information must be integrated and used with a thorough knowledge of the physiology of the living body in order to obtain optimum nutrition. There is no comparison in absolute accuracy, and if we have different forms of the same vitamin or amino acid, we must know the biological value of each form and then calculate total activity from '*in vitro*' assays. Then remains the question of digestibility and availability, but difference between total content and available content must be understood." The National Nutrition Conference held in U. S. A. in 1941, also urged improvement of the presently known chemical and biological procedures, so as to get a more accurate idea about the nutritive value of a food-stuff.

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Comparatively very little work has been done to differentiate between the total and available content of a nutrient in a food-stuff. Such data being of vital importance, work was undertaken by us to find the physiological availability of certain essential nutrients. To begin with, experiments were done on nicotinic acid from some cereals and pulses.

The physiological availability was studied from the results of two types of experiments:—(1) Urinary excretion in experimental animals and (2) *in vivo* digestion and absorption of nicotinic acid from food-stuffs.

EXPERIMENTAL

(1) *Urinary Excretion of Nicotinic acid in Rats* :—

Four adult male rats from the same litter and of almost equal weight were selected. They were first fed on nicotinic acid free diet, the composition of which was as follows :—

Pure amylum (carbohydrate)	60 per cent.
Ethanol extracted casein (protein)	20 ,,
Sesame oil (fat)	17 ,,
Salt mixture (Osborne and Mendel) (4)	3 ,,

The diet was supplemented by the following fat and water soluble vitamins *viz.*

(1) Vitamin A	100 Int. units per cent.
(2) Vitamin D	30 ,, ,,
(3) Thiamin hydrochloride ..	100 µg per cent
(4) Riboflavin	400 µg per cent.

The diet, although designated as 'nicotinic acid free diet', contained very small amount of nicotinic acid as determined chemically.

All the four rats were kept on this diet for fifteen days in metaboli cages and during the last three days, their urines were collected over concentrated hydrochloric acid every 24 hours. Nicotinic acid and trigonelline were estimated by the method of Perlzweigl, Levy and Sarett (5). A daily record of food intake was maintained.

The amount of nicotinic acid ingested during the period was determined by the following method :—

1 g. of the diet was hydrolysed by 20 c.c. of 2N HCl for half an hour. It was centrifuged and 10 c.c. of the centrifugate were decolorised by the method of Barborka and Friedmann (6). Nicotinic acid was estimated colorimetrically in an aliquot using Koenig's reaction. The colour matching with the standard was done on Klett-Summesen photometer using 4400 Å filter in place.

After this period on nicotinic acid free diet, the rats were divided into two groups: rats Nos. 1 and 3 were fed on the diet to which rice was added, while rats Nos. 2 and 4 were kept on the diet supplemented with pure nicotinic acid equivalent to that supplemented by rice to the first pair. Feeding was continued for ten days, and urine samples were again collected over HCl during the last three days, and the amounts of nicotinic acid and trigonelline were determined. Ingested amount of nicotinic acid was calculated from the intake of food by the individual rats.

The experiment was further continued by interchanging the diets. The rats Nos. 1 and 3 which received the cereal diet were given the diet with pure nicotinic acid added to it, and the rats Nos. 2 and 4 were given the diet supplemented with rice.

This procedure gave an idea about the excretion of nicotinic acid in two pairs of animals, as well as the effect on the excretion in the same pair when the ingested amount was from different sources (cereal and pure chemical).

The results of the urinary excretion experiments are shown in Table No. 1.

TABLE No. I.

Urinary excretion of nicotinic-acid in rats on different diets.

Rat No.	Fed with cereal (rice) diet.			Fed with diet* to which pure niacin was added.		
	Niacin ingested in μg/day	Niacin excreted per day.		Niacin ingested in μg/day.	Niacin excreted per day.	
		in μg	per cent. of ingested.		in μg	per cent. of ingested.
1	256.6	139.0	54.2	242.9	187.3	77.1
2	273.6	79.7	29.1	243.9	99.7	41.0
3	256.8	95.0	37.0	338.6	184.0	54.2
4	256.8	67.1	26.1	278.5	179.1	64.3

* Nicotinic acid free diet.

The above results indicated that there was more excretion of nicotinic acid of urines of rats when they were fed with pure nicotinic acid than when fed with the same amount from the cereal (rice), showing thereby that either all the nicotinic acid in the cereal was not probably set free during the process of digestion or that the nicotinic acid figures from food-stuffs by chemical assay do not represent the true vitamin content. Therefore, in order to get more precise information of a quantitative nature, 'vivo-digestion' in rats was studied.

(2) *Vivo-digestion and absorption of nicotinic acid in rats* :—

A healthy adult rat was starved for about 24 hours. It was then given light ether anaesthesia, and a known amount of the finely powdered cereal or pulse (1 g.) made into a fine paste was introduced into its stomach, as shown in the accompanying photograph.

The food-stuff was made into a fine paste and was introduced into the stomach by means of a syringe and a catheter. In every case, a small amount of the food stuff did remain in the syringe and the rubber catheter. The amount thus remaining was determined by weighing the catheter and the syringe before and after the introduction of the food paste dried at 100° C. This quantity was then subtracted from the original weight of the food-stuff used for making the paste, so as to get an exact idea of the food-stuff introduced into the stomach of the animal.

The animal was sacrificed after five hours—a period during which food is normally supposed to be digested in a normal organism. Its small intestine and stomach were washed by normal saline, and nicotinic acid in this washing was taken as the amount that had remained unabsorbed during digestion. This value was subtracted from the total nicotinic acid content of the food-stuff similarly estimated, and thus was obtained the value of the actual amount of nicotinic acid (*i.e.*, the physiologically available portion of nicotinic acid) from the cereal or pulse that was absorbed during the normal process of digestion.

The results of some such experiments are shown in Table No. II.

In this experiment, however, presumptions were made that all nicotinic acid liberated from the cereal or pulse during the period of digestion was wholly absorbed in the system, and that the rat starved for 24 hours did not possess any nicotinic acid in its intestinal residue. The validity of these presumptions was proved by suitable experiments.

Firstly, the estimations of nicotinic acid in the stomach and intestine of starved rats were carried out. For this purpose a rat was starved for 24 hours previous to its being sacrificed. It was given only water

* Refer Page No. 5.

TABLE No. II.

Vivo-digestion and absorption of nicotinic acid in rats.

Cereal or Pulse. (*a*)	Acid hydrolysis. (*b*) μg/g	niacin fed. (*c*) μg	niacin recovered. (*d*) μg	niacin liberated. (*e*) μg/g	per cent availability (*e*/*b* × 100)
Rice (Oryza Sativa)	56.5	49.0	18.9	34.0+3.25	60.1
Wheat (Triticum Vulgare) ..	72.4	70.4	13.3	58.7+3.96	81.1
Gram (Cicer Arietinum) ..	57.3	55.6	13.0	43.9+2.22	76.6
Tur (Cajanos Indicus) ..	52.2	50.0	13.9	36.6+1.67	70.1
Yeast	419.2	414.6	31.6	387.2+4.64	92.4

ad lib. After killing it, its stomach and intestine were washed with normal saline and nicotinic acid was estimated in the washings. The results are shown in Table No. III.

TABLE No. III.

Nicotinic acid in washings from stomach and intestine of rats starved for 24 hours

Expt. No.	Amount of nicotinic acid in μg in	
	Stomach washing.	Intestine washing.
1	0.7	0.9
2	1.7	1.2
3	1.0	0.6
4	0.9	0.7
5	0.6	1.2
Mean	0.98+0.4	0.92+0.24

In another set of experiments 400 μg of pure nicotinic acid were introduced into the stomach of an adult rat previously starved for 24 hours. It was then killed after five hours and its stomach and small intestine were washed with normal saline and nicotinic acid estimated in these washings. The results are shown in Table No. IV.

TABLE No. IV.

Nicotinic acid in washings from stomach and intestine of rats, five hours after giving 400 μg *of nicotinic acid in solution.*

Expt. No.	Nicotinic acid ingested.	Nicotinic acid in stomach 5 hrs. after ingestion.	Nicotinic acid in intestine 5 hrs. after ingestion.
1	400 μg	nil	nil
2	,,	0.17 μg	0.13 μg
3	,,	nil	nil
4	,,	0.14 μg	nil
5	,,	nil	nil

These experiments have shown that the presumptions mentioned above were valid, and that the rat's intestine was capable of absorbing as much as 400 μg of nicotinic acid in free condition during the period of five hours. This quantity was much higher than that employed in the *vivo-digestion experiments* (Table No. II). It could, therefore, be said that whatever amount of nicotinic acid that was set free in these experiments was completely absorbed, and the portion that remained over after five hours possibly represented the portion that could not be set free from the food-stuff during the period.

DISCUSSION

From the experiments on urinary excretion, it will be seen that in rats Nos. 1 and 2, when they were fed with the cereal (rice) diet, the daily excretion of nicotinic acid in urine was 139.μg and 79.7 μg respectively. When these animals were fed with the same amount of pure nicotinic acid as that contained in the rice diet, their daily excretion rose from 139.0 μg to 187.3 μg in one case and from 79.7 μg to 99.7 μg in the other. Rats Nos. 3 and 4 also showed a similar tendency. These findings suggested that either less amount of nicotinic acid was present in the food-stuffs than that represented by the acid hydrolysis or that all the nicotinic acid, as estimated chemically, was not set free during the digestion in the rat's intestine, and was not thus nutritionally available for the animal.

Although these experiments were elucidative of several points so far obscure to us, they did not and could not give any quantitative measure of the physiological availability of nicotinic acid in a food-stuff (rice). This was, perhaps, due to several factors, influencing the results, which could not be controlled. The most important of these is that nicotinic acid, and several other members of the B-complex, are synthesized in the intestine particularly by the rat (7, 8). For this reason, the amount of nicotinic acid estimated in urine samples of the rat represented not only the amount ingested in the food-stuff but also that synthesized in its intestine. The rate of such synthesis would depend on a number of nutritional factors. Further, the excretion of the vitamin in urine is an outcome of various metabolic processes which have not yet been thoroughly understood.

In order to obviate these difficulties and to get a quantitative measure of the physiological availability of the vitamin, different types of experiments were undertaken. It was considered that the correct approach to the problem was to find out actually how much of the nicotinic acid was liberated from the food-stuffs in a living system during the process of digestion.

Now, digestion is a process as a result of which the food that is ingested undergoes a complete change, accompanied by the liberation or production of various nutrients which are then absorbed in the blood system. The period for completion of such a process is normally taken to be about five to six hours in an animal. If, therefore, the stomach and the intestine contents are examined for the introduced nutrients, after the period, one can get a clear picture of the digestion, liberation and absorption of the nutrient. If a nutrient from a food-stuff is completely utilised, then the residue in the lumen after the digestion period is over, ought to be free from it. It would, on the other hand, contain some residual amount of the nutrient if it is not completely set free and absorbed during the digestion period. The residue in the lumen may also contain the nutrient, if the latter is set free but not completely absorbed during the digestion period. In the present case, however, it could be seen from Table No. IV that such a condition could not possibly arise, and hence the amount of the nicotinic acid in the residue might represent the physiologically unavailable portion.

One more possibility did, however, exist. It was likely that all that was determined as nicotinic acid in a food-stuff by the chemical method was not the active vitamin, and that the active portion was that which was absorbed during the process of digestion.

Whatever be the possibilities, the fact remained that the amounts of nicotinic acid physiologically available for the rat were varying in various food-stuffs. These experiments have, therefore, substantiated the belief of Elvehjem and others that there is a fundamental difference between the total content and the available content of a nutrient in a food-stuff.

SUMMARY

Experiments were carried out on rats to assess the physiological availability of nicotinic acid for the animal from cereals and pulses. They were of two types : (1) the estimation of nicotinic acid excreted in the urines of rats when the vitamin was fed from different sources and (2) the estimation of nicotinic acid utilised from a food-stuff during vivo-digestion.

The excretion experiments gave a qualitative indication that the nicotinic acid from a cereal or pulse, as determined by a chemical method, was not all 'physiologically available'. This finding was corroborated and substantiated by the vivo-digestion experiments. Quantitative data have been evolved.

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A NEW METHOD FOR THE ESTIMATION OF AVAILABLE NICOTINIC ACID FROM FOOD-STUFFS.

R. G. Chitre* and D. B. Desai*.

Methods of estimating nicotinic acid in food-stuffs have been based upon chemical or micro-biological assays. The chemical method is based upon the Koenig's reaction (1) in which nicotinic acid reacts with cyanogen bromide and aniline hydrochloride to give a coloured complex, which is then taken as the measure of the amount of the vitamin present; while the micro-biological method is based on the utilisation of nicotinic acid by micro-organisms for their growth. In both these methods, however, the preliminary treatment remains the same, namely the food-stuff has first to be treated chemically to liberate the vitamin. It is this pre-treatment that introduces various sources of error in the actual estimation of the vitamin either by the chemical or the micro-biological method.

During this treatment substances other than nicotinic acid are often liberated which are either themselves yellow coloured or which give rise to yellow coloured solutions on reacting with the reagent for nicotinic acid, and thus give higher values for nicotinic acid (2, 3, 4). Various workers have suggested different methods for removing these coloured impurities but with little success (5, 6, 7, 8). To avoid the interference of these substances, use of different amines has also been advocated by some, but so far none of the modifications has been found to be specific for nicotinic acid (9).

The micro-biological method too has its own shortcomings (10). It has been found that the unsaturated fatty acids and starch have a well-defined stimulating action for L. Casei—one of the commonly used organisms in micro-biological estimations, and hence care had to be taken to ensure their complete removal. It is also probable that unknown essential nutrients for these organisms may also co-exist.

Recently, several authors have used enzyme preparations for liberating vitamins of B-complex, particularly thiamin and nicotinic acid, from their parent sources. This method has an advantage over the chemical method of liberating the vitamin, because it is not so drastic and consequently there is less likelihood of interfering substances being simultaneously liberated.

Thus Hennesy and Cerecedo (11) used a preparation of beef kidney as a source of enzymes, which however was found to be unsatisfactory by Melnick and Field (12) who recommended dried yeast. Kinnersley and Peters (13) used takadiastase which contained takaphosphatase. Bhagwat (14) used an enzyme preparation from pig's intestinal mucosa which contained proteoses as well as phosphatases for liberating thiamin and nicotinic acid from cereals and pulses.

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It still remains to be seen whether such procedures give more accurate values for nicotinic acid, and whether these are comparable with the quantity of nicotinic acid physiologically available for nutrition. In another communication (*vide* page 471 of this issue of the Journal) we have given details of our investigation of this problem by using rat's stomach and intestinal mucosa for the preparation of enzymes. The albino rat was selected because it is cheap and easily bred in a nutritional research laboratory. It may be mentioned that, incidentally, during the course of investigation, a new method for the estimation of nicotinic acid was evolved. This method, which aims at determining the physiological availability of the nutrient, is described in the present paper.

EXPERIMENTAL

Preparation of the enzyme extracts :—

A healthy adult rat was starved for 24 hours and then killed. Both its stomach and small intestine were washed with normal saline solution by introducing glass canulae at two ends.

(*a*) *Enzyme extract from stomach mucosa :—*

The enzyme from the stomach was extracted with buffer solution of pH2 having the following composition :—

60mgs. KCl and 96 mgs. Na_2HPO_4 per 100 c.c. (16).

This was almost identical with that of the gastric juice in rat's stomach. The pH was adjusted by dilute HCl. The stomach was macerated with this solution by adding some glass powder to facilitate the process. It was then centrifuged and the supernatant liquid made up to 50 c.c.

(*b*) *Enzyme extract from the small intestines :—*

The solutions used here were of two different pH namely, pH7 and pH9, and contained NaCl and $NaHCO_3$ in almost the same percentage as is usually found in the small intestine of a normal rat (16). The small intestine was cut into two parts, and the one nearer the pyloric end of the stomach was macerated with that of pH7, and the other down to the caecum with solution of pH9. The solutions were then centrifuged and the supernatant liquids made up to 50 c.c.

Liberation of nicotinic acid from cereals and pulses using the above preparations :—

One gram of the cereal or pulse (finely powdered) was incubated with 10 c.c. of the stomach enzyme preparation for 2½ hours—the normal average period after which the food is supposed to leave the stomach. After incubation, the residue was separated by centrifuging and washed with distilled water. The washings, after centrifuging, were added to the original extract. The residue was then further incubated with the enzyme preparation from the small intestine of pH7 and 9 on the same lines, and extracts separated by centrifuging. The period of incubation was three hours.

Estimation of nicotinic acid in the extracts :—

PRELIMINARY TREATMENT :—

The enzyme extracts were first boiled with an equal volume of 2N HCl for half an hour and then filtered using Whatman No. 44. In some cases, the extracts became slightly coloured. This was especially so in the case of wheat, gram and tur. These, consequently, gave rise to higher blanks, and had therefore to be decolorised prior to the development of the colour. Only two methods of decolorisation were studied, (i) the Zn(OH)2 method of Friedmann and Barborka (5) and (ii) the KMnC4 method of Krehl, Strong and Elvehjem (8). Of the two, the latter was found to be the better, as it was more convenient and gave almost colourless solutions. The method of decolorisation, in short, was as follows :—

Aliquot (15 c.c.) was neutralised after boiling with HCl and again acidified with 1 c.c. of 4N H2SO4 and then heated with 0.5 c.c. of 1 NKMnO4 (excess being carefully avoided) at 60°-65° C for about 10-15 minutes. After decolorisation, the pH was adjusted to 6 using bromocresol—purple as external indicator.

COLOUR DEVELOPMENT :—

Each of the extracts thus treated was divided into three equal parts. One was kept in a water-bath at 70° C for 2-3 minutes, 2 c.c. of cyanogen bromide solution (4 per cent., freshly prepared) were added to it, and it was further heated at 70° C for about five minutes. It was then cooled under tap water to room temperature, and 2 c.c. of aniline hydrochloride solution (10 per cent) were added. The colour developed was read within 2-3 minutes in the lumetron photo-electric colorimeter with 4400Å filter in place. To another portion, a known amount of pure nicotinic acid was added, and the colour developed in exactly the same manner as in the first case. The third portion was used as 'dilution' blank (without the reagents). Care was taken to see that the pH of all the three parts was the same before matching the colours in the photo-electric colorimeter. Besides the 'dilution' blank, a 'reagent' blank was also run.

CALCULATIONS :—

The co-efficient of extinction for different solutions was found and by applying the necessary blank corrections, the extinction co-efficients for the known amount of nicotinic acid added to the test solution, and for the test solution, were determined, and the amount of nicotinic acid in the test solution was then calculated.

Table No. 1 shows the results of estimations carried out by this method.

TABLE NO. 1.

Nicotinic acid content of food-stuffs by acid and enzymic hydrolysis methods.

Cereal or pulse.	Acid hydrolysis.	Expts. in vitro-enzyme hydrolysis			
		pH 2	pH 7	pH 9	Total.
Rice (Oryza Sativa)	56.5	27.7	nil	nil	27.7 ± 2.51
Wheat .. .. (Triticum Vulgare)	72.4	29.8	nil	nil	29.8 ± 1.48
Gram .. .. (Cicer Arietinum)	57.3	52.5	nil	nil	52.5 ± 3.14
Tur .. .. .. (Cajanus Indicus)	52.2	35.9	nil	nil	35.9 ± 2.23
Yeast	419.2	263.8	nil	nil	263.8 ±2.54

During the process of estimating nicotinic acid by this method, different steps taken involved incubation, filtration, addition of various decolorising agents and so on. It was thought likely that during one or all such procedures the vitamin might have undergone destruction. These points were, therefore, first studied separately.

(1) *Effect of incubation :—*

In the above experiments, cereal or pulse was incubated with solutions of different pH for a period varying between 1½ to 2½ hours. Therefore it had, first of all, to be seen whether incubation had any deleterious effect on nicotinic acid present in the enzyme extract. This was elucidated by performing experiments with pure nicotinic acid and conducting recovery experiments. A known amount of nicotinic acid was added along with a certain weight of a cereal (rice), to a series of solutions of various pH used. These were then incubated for 2½ hours. Corresponding controls were kept without incubation. The residue of the cereal was removed by centrifuging, and nicotinic acid estimated in the supernatant solutions. Results are shown in the Table No. 2.

TABLE No. 2.

Effect of incubation on pure nicotinic acid.

pH	Expt. No.	Amount of nicotinic acid in control series.	Amount of nicotinic acid in incubated series.
2	1	16.8 µg.	16.1 µg.
	2	15.3 µg.	15.7 µg.
	3	16.2 µg.	16.2 µg.
7	1	32.5 µg	32.0 µg.
	2	31.3 µg.	32.5 µg.
	3	16.1 µg.	16.1 µg.
	4	31.4 µg.	30.7 µg.
9	1	29.1 µg.	28.7 µg.
	2	32.1 µg.	31.4 µg.
	3	16.1 µg.	15.4 µg.
	4	33.0 µg.	33.2 µg.

The recovery experiments have shown that nicotinic acid is not destroyed under the experimental conditions.

(2) *Effect of filtration :—*

On adjusting their pH, the enzyme extracts became turbid and had, therefore, to be filtered. Of all the filter papers, Whatman No. 44 was found to be the most suitable, as the filtrate obtained was very clear. However, some workers have contended that filter paper absorbs nicotinic acid (Bandier and Hald (6). It was, therefore, thought necessary to verify this in the case of Whatmann filter paper. This was accomplished by performing a few experiments as follows :—

Two sets of solutions were taken. In one set, nicotinic acid was added before filtration and in the other after filtration. The final volumes of solutions were kept the same.

TABLE No. 3.

Absorption of pure nicotinic acid by Whatmann No. 44 filter paper.

H	Expt. No.	Coefficient of extinction	
		niacin added before filtration.	niacin added after filtration.
2	1	0.1539	0.1539
	2	0.1842	0.1857
7	1	0.2508	0.2508
	2	0.1575	0.1575
9	1	0.1555	0.1523
	2	0.1602	0.1602

From the table No. 3 it could be seen that there was no absorption by filter paper Whatmann No. 44 under the experimental conditions.

(3) *Effect of hydrolytic products on colour development* :—

The Koenig's reaction is dependent upon various factors, and among these, the presence of certain ions in the solution is of importance. It has been shown by Bandier and Hald (6) and Kodicek (3) that ions, such as acetate and bicarbonate, have a definite effect on the colour development. In the present series of experiments, it was possible that one or more of such interfering substances were present in the solutions during the course of enzyme hydrolysis, in addition to some which might have resulted from the enzymic degradation. The nature of the latter is, however, unknown. In order to see the effect of such substances on the development of nicotinic acid colour, a series of experiments were undertaken.

Three series of test solutions were examined (*a*) hydrolysate from a food-stuff, (*b*) hydrolysate from food-stuff to which a definite amount of nicotinic acid was added, and (*c*) distilled water to which the same amount of nicotinic acid as in (*b*) was added. Colour was developed in the usual manner, and readings taken. The difference between the readings for (*b*) and (*a*) was compared with the reading for (*c*). This procedure gave an idea of the effect of hydrolytic products concerned in the method. The results are shown in table No. 4.

TABLE No. 4.

Effect of hydrolytic products on the colour development of pure nicotinic acid with its reagents.

Test solution. (hydrolysate from)	Readings due to nicotinic acid in test solutions.			
	a	*b*	*b-a*	*c*
Rice (Oryza Sativa)	71	134	63	32
Wheat (Triticum Vulgare)	97	160	63	32
Gram (Cicer Arietinum)	48	100	52	34
Tur (Cajanus Indicus)	42	93	51	34

It will be seen from the table No. 4 that the readings due to the amount of nicotinic acid in different solutions were different, and hence it was essential to prepare, each time, standard by adding pure nicotinic acid to the test solution, rather than calculate the value for niconitic acid by referring to a standard graph. This procedure was followed throughout the experiments.

(4) *Decolorisation of acid hydrolysates from food-stuffs :—*

It has been already mentioned that of all the methods of decolorisation, only two were studied in detail : one in which $Zn(OH)_2$ was used as the substance absorbing the colouring matter (Friedmann and Barborka, 5) and the other in which $KMnO_4$ was used for oxidising the interfering colouring matter (Krehl, Strong and Elvenhjem, 8).

In order to determine which of these two methods was more efficient in giving colourless solutions, the following experiment was performed :

A part of the hydrolysate from a cereal or pulse was decolorised by $Zn(OH)_2$ and another by $KMnO_4$ method. After decolorisation, the pH of both was adjusted to 6. The aliquots of the solutions thus treated were taken so that each of them contained the same fraction of the original hydrolysate. They were then made up to equal volumes, and readings of the colour taken on a photometer. These readings were compared with the readings of the colour of the original untreated hydrolysate diluted to the same extent with distilled water. Table No. 5 shows the photometer readings for these solutions.

TABLE No. 5.

Decolorisation of the hydrolysates by $Zn(OH)_2$ and $KMnO_4$ methods.

Cereal or pulse.	Untreated hydrolysate reading.	$Zn(OH)_2$ treated		$KMnO_4$ treated	
		reading.	% decolorisation.	reading.	% decolorisation.
Rice..	30	27	10	6	80
Wheat	59	49	17	6	90
Gram	63	54	14	6	90
Tur	72	58	19	5	93

It could be seen from the table No. 5 that the $KMnO_4$ method of decolorisation was the better of the two.

Before adopting this procedure, it was further essential to see the effect of $KMnO_4$ on nicotinic acid and recovery experiments were, therefore, performed by adding pure nicotinic acid to the hydrolysates before decolorising.

A cereal or pulse was hydrolysed with 1N HCl. The hydrolysate was centrifuged and divided into two portions (*a*) and (*b*). To (*a*) was added 1 c.c. of pure nicotinic acid solution (8 µg) and to (*b*) was added

1 c.c. of distilled water. These solutions were decolorised by the above method, and nicotinic acid was estimated in both. The difference between the two gave the amount of added nicotinic acid recovered at the end of the experiment. The results are shown in table No. 6.

TABLE NO. 6.

Results of nicotinic acid recovery experiments.

	Rice.	Wheat.	Gram.	Tur.
Amount of nicotinic acid added	8.0 μg.	24.0 μg.	8.0 μg.	8.0 μg.
Amount of nicotinic acid recovered	8.2 μg.	23.5 μg.	8.3 μg.	8.3 μg.
Percent recovery	102	98	103	103

The recovery was almost 100 per cent and it could, therefore, be inferred that the method employed involved no loss of nicotinic acid.

(5) *Effect of pH on the blank reading* :—

H-ion concentration has been found to have a definite effect on the colour intensity of the complex of nicotinic acid with the reagents (17) and it has, therefore, been suggested that the pH of the solution be adjusted to 6-7 before developing the colour. But during the course of the present investigations, another point was observed that when the test solutions contained an appreciable amount of residual colour, its pH exerted a considerable influence on its colour intensity. It was found to increase with greater alkalinity and to decrease with increasing acidity. When the colour was developed in the solution with the reagents (cyanogen bromide and aniline hydrochloride) the pH of the solution though initially 6 became more acidic on account of the acidity of aniline hydrochloride, and the residual colour got discharged to a certain extent. If, therefore, at the same time the pH of the blank were not adjusted the same as that of the test solution, the blank reading (due to the presence of the residual colour) was likely to remain high, thereby introducing an error in the photometric reading of the blank, and consequently in the amount of nicotinic acid estimated. The table No. 7 will illustrate the discrepancy due to different pH of blank and the test solution.

The table No. 7 indicated the importance of equalising the pH values of the blank and of the test solution after development of the colour.

Another point that had to be elucidated was whether the extraction of the vitamin from the food-stuff by this method was complete. In order to verify this, an experiment was performed with the liver of a

TABLE No. 7.

Effect of pH on the blank readings for hydrolysates from cereals and pulses.

Cereal or pulse.	pH adjustd to 6.	pH adjusted to that of the test solution.
Rice	125	15
Wheat	32	17
Gram	34	18
Tur	37	20

rat, which is a good source of nicotinic acid (as well as of its amide) and which is, at the same time, free from the interfering pigments which the cereals or pulses contain. Nicotinic acid was liberated both by acid as well as by enzyme hydrolysis, and estimated by the above procedure after decolorising the hydrolysates with KMnO4. The value for both the hydrolysates agreed fairly well (table No. 8) thereby showing that the enzyme hydrolysis was able to extract the vitamin completely from such sources.

TABLE No. 8.

Nicotinic acid content of rat's liver by acid ad enzyme hydrolysis. (in ug./ g.)

Liver No.	Acid hydrolysis.	Enzyme hydrolysis.
1	145.8	144.8
2	124.8	121.6

DISCUSSION

It will be seen that the conditions under which the liberation of nicotinic acid, in these experiments, was carried out were in conformity with those actually present during the normal process of digestion. Thus, the food-stuff was first acted upon by the stomach enzymes and then subjected to the action of the intestinal enzymes. The pH values and the composition of the buffers used were also as far as possible similar to those of the digestive juices in a rat. The periods of incubation with the enzyme preparations were also the same as those of the corresponding stages in the process of digestion. The method was thus rendered significant, from the physiological point of view, by maintaining the conditions comparable with those existing in the normal process of digestion. This method differed from that of Bhagwat (14) who used only the intestinal enzymes (from pig) in a buffer solution of pH 7 for liberating nicotinic acid (and thiamin) after 24 hours. Values of nicotinic acid by the two methods, therefore, showed slight variations.

The second significant point in this method was the agreement with the values obtained by the method of vivo-digestion described elsewhere (15). The table No. 9 shows the points of agreement on statistical analysis, except in the case of yeast.

The marked difference shown by yeast in its value for nicotinic acid by these methods, might be due to this-that yeast perhaps contains a substance which is released by the acid hydrolysis, which might be interfering with the colour development of nicotinic acid with its reagents giving higher values for it. Further, such a substance if present was not evidently destroyed during the course of decolorisation by $KMnO_4$. In the process of digestion this substance, however, might have undergone such a change, either by being absorbed or otherwise, that it was absent in the residue collected after digestion, and therefore did not interfere with the colour development when nicotinic acid was estimated in the residue. It is not possible at this stage to assert anything about its nutritional value. It may not be of any significance from the point of view of nutrition. That such a substance may be the 'precursor' of nicotinic acid (18) is ruled out on the ground that the precursor is water soluble and hence ought to be present both in the enzyme as well as in the acid extract. The existence of such a substance in some food-stuffs cannot be finally accepted unless more convincing experimental evidence is forthcoming.

TABLE No. 9.

Nicotinic acid content of food-stuffs by in vitro and in vivo experiments.

Food-stuff. (a)	Mean value by vitro expt. in µg./g. (b)	Mean value by vivo expt. in µg./g. (c)	Diff. (b-c) (d)	Std. error of diff. bet. the means (d) (e)	Rati. d/e (f)
Rice	27.7+2.51	34.0+3.25	+ 6.3	+4.1	1.5
Wheat	29.8+1.48	58.7+3.96	+28.9	+4.0	7.2
Gram	52.5+3.14	43.9+2.22	+8.6	+4.0	2.1
Tur	35.9+2.23	36.6+1.67	+0.7	+2.8	0.3
Yeast	263.8+2.54	387.2+4.64	+123.4	+5.3	23.8

The amount of nicotinic acid in cereals and pulses, as estimated by this method, was considerably less than that obtained by the usual acid hydrolysis procedure. These lower values might very well be attributed to the method followed in these experiments for liberating the vitamin from its sources. The acid hydrolysis method has been found to be more drastic by various workers. In such methods, the food-stuff is boiled with strong HCl as a result of which, along with nicotinic acid, other chromogenic products are liberated which, either alone or with the reagents used (cyanogen bromide and aniline hydrochloride) for estimating nicotinic acid, give higher values for the vitamin in the food-stuff. On the other hand, the procedure followed in these experiments for liberating nicotinic acid is not so drastic. Consequently, there is less likelihood of products other than nicotinic acid being co-liberated with it.

We may, thus, consider ourselves justified in concluding that the values for nicotinic acid obtained by this method represent a more correct approximation to the real amount actually available for nutrition, and the figures given for nicotinic acid express the true 'physiologically available' nicotinic acid.

SUMMARY

(1) A new method of estimating the amount of nicotinic acid has been described, making use of the stomach and intestine enzymes of an adult albino rat for its liberation from food-stuffs.

(2) Various factors influencing the colour development of nicotinic acid with the reagents, such as the effect of incubation with the enzyme solutions, filtration, hydrolytic products, and the H-ion concentration, have been studied.

(3) The amount of nicotinic acid estimated by this procedure was found to agree fairly well with that obtained by experiments on vivo-digestion in rats. Thus, the figures for nicotinic acid obtained by this method could be said to represent, 'true physiologically available' nicotinic acid.

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CHEMOTHERAPY IN CANCER

An Evaluation Of Some Recently Introduced Chemical Agents

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It has been the dream of every physician who has had to deal with the ravages of cancer to possess a drug which could gradually melt away cancerous tumours and restore the patient to health. While so far this has remained only a dream, the discovery in recent times of therapeutic agents potent in other fields, like the sulphonamides and penicillin, has aroused optimism as regards the possibility of finding such a remedy for cancer, and further stimulated active research in that direction. From time to time the cry "Eureka" has been raised, and the lay press has shouted in its headlines that a cancer cure has been found. Great hopes have been raised particularly in the hearts of cancer sufferers and repeatedly these hopes have been cruelly crushed. The responsibility for these recurring tragedies has to be placed at the door of the sensational press and the unscrupulous advertising campaigns of interested parties. So many cancer cures have recently been featured in the press, and so much misinformation appears to exist about them, that this review of the scientific literature relating to them has been undertaken in order to enable the practising physician to correctly appraise them.

Many chemical agents have recently come into use in the treatment of cancer. None of them has been known to cure cancer. But many of them have proved to be of great benefit in the palliative management of the disease. The most valuable of these are the estrogens which have achieved remarkable results in prostatic cancer, and the androgens which have proved to be of considerable value in the treatment of bone metastases of mammary cancer. About the uses and limitations of these hormones very definite ideas exist; but the physician is apt to be confused by conflicting reports about other chemical agents that attract his notice in the lay press, the advertising bulletins of commercial drug houses, and references in medical literature. It is, therefore, proposed to confine this review to these latter preparations, and to leave the consideration of the estrogens and androgens to a subsequent number.

H-11

H11 is an extract prepared from male urine, and since 1941 has been given much publicity by the Hosa Laboratories where it is prepared. Thompson, the discoverer of H11, claims that it has an inhibitory action on malignant tumours, basing his conclusions on his experiments on the Twort carcinoma in mice, and the treatment of human beings. Thompson and his associates have published papers [34], [43] about the good effects of H11. However, confirmation of these results has not been forthcoming from other workers. On the contrary other investigators have found no inhibitory effect whatever on malignant tumours[14,48]. Gye,[14] Director of the Imperial Cancer Research Fund, tested the value of H11 on animal cancer (mouse mammary carcinoma M 63). His conclusions were that H11 had no growth inhibitory effects on the tumours used in his experiments. Thompson[44] objected that Gye's research was irrelevant as the Hosa Laboratories claimed inhibitory effects on the Twort carcinoma only. But it is well known among research workers in this field that the Twort carcinoma of the mouse is a very unstable tumour and liable to spontaneous regressions, and so is not a suitable tumour to use for these experiments.

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Woodhouse[48] in 1943 published his experience with H11 on two other transplanted malignant tumours, and also on the mouse carcinoma M 63 used by Gye. He summarised his results thus: "In 54 mice bearing grafted dibenzanthracene sarcomas, carcinoma 63, or induced benzpyrine skin epitheliomas, no inhibitory effect on the tumour growth was found after prolonged injections of the urine preparation, H11. Two sarcomas removed from mice after such injections were successfully grafted into other animals, and histological examinations of treated tumours showed no difference from control material."

The claims of the Hosa Laboratories have been so insistent and so widely advertised that the Medical Research Council of England decided to appoint a committee to investigate them. This committee commenced a systematic study in 1944 and set about the enquiry in three directions: 1. A study of the clinical case-records supplied by the Hosa Laboratories in order to find out the results of administering H11 to patients suffering from cancer. 2. An experimental investigation into the effect of H11 upon malignant tumours in mice. 3. A careful examination of all the available literature on the subject. This committee has recently issued its report[23] in October 1948, which is summarised below.

Of the 3000 case records kept by the Hosa Laboratories, 1000 random cases were transcribed on special forms and studied by Dora Colebrook with the co-operation of Ollerenshaw of the Hosa Laboratories. An examination of 139 random forms immediately showed that the criteria used by the Laboratories to judge the effect of H11 on human patients were fallacious, the follow up of the patients was very inadequate, and what is more the records did not qualify for a scientific statistical analysis. After a prolonged study of the analysis of the Hosa case sheets referred to above the conclusion the committee reached is that "it is unable to infer, from the Hosa records, that the administering of H11 to these patients did in fact have any effect on the growth of the cancer or prolong the life of the patients."

With regard to the effect of H11 on experimental tumours, on account of Thompson's objection to Gye's experiments, the committee appointed Georgiana M. Bonser, Brotherton Fellow in Cancer Research in the University of Leeds, to undertake a long and laborious series of experiments. She used both the Twort carcinoma, insisted upon by Hosas, as well as mice grafted with spindle cell sarcoma, and mice bearing spontaneous mammary cancer. Her conclusions confirm the report by Gye, and also show that there is no evidence that H11 had any growth inhibitory effect in any of the experiments carried out.

The final conclusions of the committee are summarised thus: 1. It has not been possible to deduce from the analysis of the Hosa records that H11 has any effect either on the rate of growth of cancer in man or the clinical course of the disease. 2. So far as the experiments on mice carried out under its direction are concerned, no inhibitory action by H11 has been demonstrated.

Needless to say the Hosa Laboratories have published a reply[38] to the report of the committee complaining that the methods of assessment used by the committee were not suitable to this type of investigation and, therefore, their report was not a fair judgment on H11. It is, however, difficult to imagine that a committee made up of scientific men of repute that has taken 4 years to examine the data, and also gone to the expense and trouble of conducting an exhaustive series of experiments on mice, should be activated by any motive but that of a true scientific appraisal of an alleged cure for a dread disease.

ANTIRETICULAR CYTOTOXIC SERUM (A.C.S.)

Bogomolets (1943),[2] a Soviet scientist, reported on the beneficial effect of A. C. S. in malignant disease, with reduction of pain, improvement of the general condition of the patient, and even some regression of metastatic tumours. A. C. S. is an anti-serum produced by using material from the human spleen as an antigen in rabbits. Other investigators have confirmed that there is frequently an improvement in the general condition of the patient, but have shown that A. C. S. has no inhibitory effect on the cancer. Skapier[41] tried A. C. S. on 22 patients of Hodgkin's disease. Ten, who were treated with A. C. S. alone, showed progressive decrease in the sedimentation rate and final return of the rate to normal. Eleven patients had a rise in the haemoglobin level. Gain in body weight occurred in 12. Only in one case was there an appreciable decrease in size of a tumour (retroperitoneal). He concludes that A. C. S. did not prove to be a curative agent in Hodgkin's disease, but as there was an improvement in the general condition in the majority of the cases, A. C. S., may be considered an useful adjunct in the treatment. Davis[6] in a preliminary report on 106 cases, observed the same general improvement but no appreciable prolongation of life.

K-R

Two years ago a great stir was made in the newspapers about a Russian discovery of a cancer cure by Roskin and Klyueva. So much newspaper publicity was given to this preparation (called K-R after the discoverers) that some of our patients even requested us to write to the Russian Government to make this new remedy available to us in India.

K-R is an "endotoxin" obtained from the micro-organism *Trypanosoma cruzi.* In an attempt to study the influence of various infections and toxins on transplanted cancer, Prof. G. Roskin[40] of the University of Moscow selected the *Trypanosoma cruzi* because of its ability to produce a chronic form of trypanosomiasis. He discovered that transplanted cancers either did not develop or grew feebly in mice infected with the trypanosomes. Other trypanosomes did not have the same effect, so that this action of *Trypanosoma cruzi* was specific. Preparations made from the killed trypanosomes ("endotoxins") had a similar effect. These and other controlled experiments on mice led Roskin to believe that he had discovered a substance that could inhibit the growth of cancer cells specifically. The "endotoxins" were then tried on 3 patients of cancer of the pharynx who were rejected by the radiotherapist. A series of injections were given into the tumour, and in one case such improvement had occurred in the size of the primary and metastases that the patient was subsequently accepted for radiotherapy, and kept well under observation for 2 years. Roskin suggested that this form of therapy deserved further trial.

Malisoff[31], in New York, is the only worker who has reported a verification of the findings of Roskin and Klyueva. He used the endotoxin of *T. cruzi* on the spontaneous mammary carcinoma in mice, and the sarcoma 180 of mice. But his work has been repeated by Hauschka and Goodwin[20] and in the identical strain of sarcoma 180 used by Malisoff, they found 50 per cent spontaneous regressions. As Malisoff's report was based on only 43 mice treated and 15 controls it is more than probable that all his regressions were spontaneous and not significant. Hauschka and Goodwin[20] also performed an exhaustive series of experiments with 8 different strains of *T. cruzi,* including that used by Roskin, and 5 varieties of malignant tumours, using altogether 1300 experimental mice. They concluded that "from the available evidence tumour inhibition by living *T. cruzi* does not appear to be a specific phenomenon, but can more adequately be attributed to a competition for essential dietary factors and to general depletion of the host system by the infection." In fact they found that when the trypanosomal infection was controlled by the specific quinoline derivative, Bayer 7602, the previously inhibited tumours resumed their usual rate of growth. No further reports on K-R are available, and in view of Hauschka's exhaustive experiments no further trials seem to be indicated.

URETHANE

Experimental work by Haddow & Sexton[15] in England showed that urethane (ethyl carbamate) had an inhibitory effect on spontaneous mammary tumours in mice, and the transplanted Walker carcinoma 256 in rats. As a result of this experience Paterson, Haddow *et alia*[35] tried the drug on malignant tumours in man. In many of these patients a fall of the leucocytic count was noticed. This prompted a trial of urethane in patients with leukaemia. They reported[35] their experience with 32 cases of leukaemia (19 myeloid and 13 lymphatic) and concluded that most cases responded favourably. There was a fall in the total white cell count, the abnormal cells being most affected, a diminution in the size of the spleen and of the enlarged lymp nodes, and a rise in the haemoglobin level. All this was remarkably similar to the effects of standard roentgen therapy. However, there was no indication that permanent benefit might be obtained, for relapses took place. They also noticed temporary improvement in some metastatic lesions in advanced breast cancer with the use of urethane. There was healing of a carcinomatous ulcer in one case. But all the patients died subsequently from advancing metastases in other parts of the body.

The usual dose of urethane is from 30 to 60 grains daily for from two to six weeks. The dosage has to be regulated by noting the effect on the blood count. Occasionally a severe depression of the bone marrow resulting in death has occurred (Webster)[47] but with care these hazards may be avoided.

Urethane, therefore, is an useful palliative in myeloid leukaemia. In the treatment of Hodgkin's disease, lymphosarcoma and other metastatic tumours no consistent results have been obtained.

RADIOACTIVE ISOTOPES

In recent years developments in atomic fission have placed a large number of radioactive substances in the hands of the physician. Not only do radioactive isotopes promise help in the solution of the mysteries of metabolic processes, but seem to open up a new field in cancer therapy of immense possibilities. The radiotherapist had long found that in certain diseases a sort of spray radiation over the whole body was of great value. In radioactive isotopes of elements that circulate throughout the body or are taken up by certain specialised tissues, has been found a source of long continued low grade radiation which is devoid of the difficulties of using the Xray machine for the same purpose.

One of the first isotopes to be used was radioactive phosphorous (P^{32}) because it was one of the products of the cyclotron which until recently was the only source of radioactive isotopes. With the discovery of the chain reacting Uranium pile, a new source of isotopes has come into being, and many more substances will make their appearance in this therapeutic field. The only isotopes that are likely to prove of value will be those that have the following characteristics : 1. A "half-life" of a few days so that the radiation may not be so prolonged as to be dangerous, or so brief as to be ineffective. 2. A selective absorption by, or deposition in, certain tissues of the body where the radiation may be concentrated. 3. A cost of production and transport that is not too high.

RADIOACTIVE PHOSPHORUS. One of the earliest isotopes to be prepared by the cyclotron, radioactive phosphorus (P^{32}) has found its greatest use in polycythaemia rubra vera and in leukaemia, in the last ten years. P^{32} has a "half-life" of 14.3 days (much over the optimum which may be said to be 7 days) and has a steady rate of decay. By giving off an electron as beta radiation it is converted to stable sulphur. The phosphorus salts are especially deposited in the bone marrow and therefore exert their best effects on the elements of that tissue.

In polycythaemia, most observers are agreed that treatment with P^{32} is the method of choice [37], [3], [36], [17], [7], [8]. But Hahn[16] believes that, as in most cases this disease can be adequately controlled by phlebotomy, it is not advisable to use an agent that might produce damage to the haemopoeitic tissues. Hall and Watkins[17] report on their experience of P^{32} in polycythaemia vera with 54 patients followed from over nine months to 4½ years. The most striking improvement was noted in the group of symptoms attributable to increased blood volume, *viz.*, headache, a sense of pressure in the head, dizziness and visual disturbances. There was generalised amelioration in all the other features of the disease. The duration of the remissions was variable : 3 of their patients had remissions lasting for over 3 years. Fifteen of the 54 patients had 2 courses and 6 of the fifteen had 3 courses. Fifty-one of the 54 patients are alive. Two, of the three who died, succumbed to acute leucopenic myelogenous leukaemia, and subacute monocytic leukaemia (Naegeli type) respectively. These authors are, therefore, inclined to believe that patients of polycythaemia treated with P^{32} run a greater risk of developing acute leukaemia, than the average man.

In chronic myelogenous leukaemia the effect of P^{32} is similar to that of X-radiation. There is reduction in the size of the spleen, a fall of the leucocyte count and a rise in the haemoglobin level. P^{32} is usually supplied as an isotonic solution of dibasic sodium phosphate with a known charge in millicuries per cubic centimetre. It is best given intravenously in doses of 1 or 2 mc. twice a week until the W.B.C. count has begun to fall. If used orally, 25% of the radioactive element is lost in the faeces. The total dose required varies from 5 mc. to 25 mc. in individual patients. Warren[45] gives an excellent review of the use of P^{32}. On the basis of 88 cases treated he concludes : No harm resulted in the doses used ; no damage to red cell formation occurred in patients not suffering from polycythaemia vera ; megakaryocytes were apparently not affected, some cases actually showing an increase in the platelet count; radiation sickness was rare as compared with X-ratiation ; practically all the P^{32} injected intravenously was excreted by the kidneys; it would be wiser to withold P^{32} in cases in whom extensive bone marrow infiltration was present as it would be likely to produce aplastic anaemia. P^{32} as a treatment for chronic myelogenous leukaemia is an useful palliative rather than a curative agent.

In chronic lymphatic leukaemia the response to P^{32} is as poor as to X-rays, though remissions in some cases may occur. In the acute leukaemias of all types the results with P^{32} have been uniformly bad in the experience of all observers [4, 9, 26, 27, 28, 29, 36, 45, 46].

P^{32} has also been tried in multiple myeloma and Hodgkin's disease without much success. In the former occasional reduction of pain has occurred. In Hodgkin's disease X-rays are preferable.

Therefore it is clear that P^{32} is not any better than X-rays in the fields in which its greatest usefulness lies. It has, moreover, the disadvantages of the difficulties of manufacture and transport, and of accurate regulation of the dosage.

RADIOACTIVE IODINE. The selective deposition of radioactive iodine in thyroid tissue was first demonstrated by Hertz, Roberts & Evans[21] in 1938. Similar studies in normal human thyroids and in goitres were reported by Hamilton & Soley in 1940 [18, 19]. They found that in the two thyroid cancers in their material, the amount of radioactive substance picked up was only 1 per cent of that taken up by normal thyroid tissue. The exact anatomical location of the radioactive material in thyroid tumours has been studied by the method of radioautography . Thin paraffin sections prepared rapidly are de-paraffinised and placed against the emulsion surface of a photographic film for adequate intervals of time ; the plates are then developed and the sections stained with haematoxylin and eosin ; the areas of darkening in the plates are then compared with the histological pattern of the sections. Adopting this method, Marinelli *et al.*[32] of the Memorial Hospital, New York, studied the take up of radioactive iodine by thyroid cancers in 19 patients. They observed that only certain types of thyroid cancers possess the ability to accumulate this substance, and that this ability appears to be closely linked with certain structural qualities, particularly, orderly cell arrangement in follicular pattern and the presence of colloid material. On the basis of these findings, and the estimation of the relative frequency of the various types of thyroid cancer they believe that, approximately only 15 per cent of thyroid malignant neoplasms may be expected to accumulate radioactive iodine in some degree.

This substance promises to have its greatest usefulness in metastatic thyroid tumours particularly of the functioning type. All the 5 cases of metastasizing goitre, in the above series, showed considerable accumulation of radioactive iodine. Frantz. Quimby and Evans[11] observed that metastatic thyroid cancers could be made to function and take up radioactive iodine if a total thyroidectomy was performed. In this way much less radioactive iodine need be used and so its ill effects are reduced to a minimum. In their series, every case of the so-called benign metastasizing goitre showed a microscopic focus of cancer in the remnant of the thyroid removed surgically, at a later date, with the idea of performing an elective total thyroidectomy for treatment of the metastatic foci with I^{131}.

TEROPTERIN

In 1945 Lewisohn and his co-workers[30] reported on the influence of "folic acid" on the growth of spontaneous breast cancers in mice. Intravenous injections of crystalline Lactobacillus casei factor led to complete regressions of these breast cancers in about one-third of the mice. At that time, the substance used for these experiments was thought to be folic acid, but later it was shown that it was really a conjugate of folic acid, pteroyl-triglutamic acid (teropterin). Working with the same material both Sugiura[42] and Zahl[49] were not able to confirm these findings of the Lewisohn group.

Sydney Farber *et alia*[10] have reported the result of their experience with the use of teropterin on a series of 90 patients suffering from various malignant diseases, in whom other therapeutic measures gave no hope. The dosage they recommend is, daily, 20 mg. intravenously, gradually raised to 50 mg. for 2 or 3 weeks. There were no untoward effects of any sort. On the basis of their experience the authors say that many patients experienced improved energy and appetite, and a sense of well being. In a few there was definite diminution of pain, and an occasional case showed histological changes in the tumour that could be attributed to the therapy. However, the authors[10] themselves say that they cannot yet present evidence that these substances should be employed in the routine therapy of cancer. Further trials are in progress. The results so far reported are couched in such vague terms that the only conclusion one can come to is that there is no definite and consistently confirmed objective evidence that teropterin has influence on malignant neoplasms. It cannot be considered a cure for cancer, but perhaps its use to help in improving the general condition of the patient may be justified.

NITROGEN MUSTARDS

With the advent of World War II research in offensive chemical agents was stimulated, and it was found that mustard gas, bis (*beta*-chlorethyl) sulphide, and its nitrogenous analogues, bis and tris (*beta*-chlorethyl) amines, had not only a local vesicant action, but also profound cytotoxic effects, especially on tissues showing a high degree of proliferating activity. As a result of this knowledge, these nitrogen mustards were tried in neoplastic malignant disease in patients, first by Gillman[12] and his associates in 1942-1943, and subsequently by others. Their results could not be published during the war for military reasons The first official statement about this work was made by Rhoads[39] in 1946, and he summarised the observations made until that time as follows :—

1. Methyl bis (*beta*-chlorethyl) amine is preferable to the tris-compounds as venous thrombosis is less likely to follow with the former.

2. The dose recommended is 0.1 mg. per kilogram of body weight intravenously, on four successive days.

3. The toxic effects are : (a) severe local inflammatory reaction if the material escapes into the perivenous tissues ; (b) nausea and vomiting of varying degree, often very severe ; (c) leucopenia, rarely agranulocytosis, normocytic anaemia, and thrombocytopenia with bleeding tendency.

4. The nitrogen mustards are not a cure for such neoplastic diseases as have been studied. The tumour regressions induced are temporary of a few months duration. The effects are in many respects similar to those of X-rays, though the great advantage of radiation therapy is that it can be given locally.

5. The best effects of these compounds seem to be on Hodgkin's disease, with disappearance of fever and gain in weight and general improvement. This, however, has continued only from two weeks to a few months and is followed by a fairly rapid relapse which may or may not respond to further therapy.

6. Results with leukaemia, lymphatic and myeloplastic, lymphosarcoma, and with a miscellaneous group of malignant neoplasms have been discouraging, except in carcinoma of the lung in which further trial is warranted.

Several reports from observers in England and America have appeared in the last 2 years and these have confirmed the statement recorded above. Jacobson[24] *et alia* and Goodman *et alia*[13] investigating the effects of these nitrogen mustards all found beneficial effects in Hodgkin's disease, in some cases of lymphososarcoma, in giant follicular lymphoma, and polycythæmia rubra vera. ApThomas and Cullumbine[1] at Manchester studied the effect of these compounds on 21 patients of

Hodgkin's disease. They preferred to give two injections each of 0.2 mg. per kilogram of body weight at 24 hour intervals, as with this technique the period of vomiting was shorter. The dose was dissolved in 20 c.c. of normal saline and courses were repeated at intervals of 6 to 8 weeks with a larger dose, of 0.3 mg/kilogram on each day. All the 21 patients improved after the first course, but many of them had a recurrence soon. Of 13 patients who had two courses 12 showed improvement after the second course and of four who had three courses only two improved. The disease appears to respond well at first but gradually becomes more resistant. Comparing these results with those in 20 patients treated by radiotherapy selected at random, it was seen that whereas the mean period of remission after one course of radiotherapy was 9.5 months, the patients treated with the nitrogen mustards required a second course in two months. It seems, therefore that radiation has to be preferred as a first treatment in Hodgkin's disease.

The experience with the nitrogen mustards at the Tata Memorial Hospital has been the same. The drug was tried in 3 cases of Hodgkin's disease, the dose used being 0.1 mg. per kilogram of body weight intravenously, on four consecutive days. All 3 patients had severe vomiting on all the four days. A diminution in the size of the lymph node masses was noticed two days after the beginning of the treatment, and in one patient a mass of nodes in the supraclavicular region of the neck completely subsided in a week. In this latter case, however, the nodes returned to their previously enlarged state at the end of 3 weeks, and it was necessary to resort to deep X-rays to control them, as there was too severe a depression of the haemopoetic system to permit a second course of nitrogen mustard. The other two cases had longer remisions before relapse, but they also suffered from an extreme anæmia, levcopenia and thrombocytopenia which persisted for several months before their death.

Craver[5] of Memorial Hospital, New York, discusses his extensive experience of the nitrogen mustards. Between 1944 and 1947 he had treated 300 patients, 239 of these belonging to the leukaemia-lymphoma groups (102 patients with Hodgkin's disease, 65 with leukaemia, and 66 with lymphosarcoma). Craver found that, in many cases, it was advisable to exceed the usual dose of 0.1 mg. per kilogram of body weight on four consecutive days. He often gave 6 to 7 times such single doses. The dosage most commonly used in recent months was a double dose of 0.2 mg./kilogram on two successive days, followed, in some cases, by a similar dose on the third, fourth or fifth day. The patient felt no worse than after the 0.1 mg./kg. dose and it shortened the period of hospitalisation. The dosage is guided mainly by the total white cell count, owing to the severe leucopenia which follows its administration. The toxic effects are the same as those described above. Nausea is felt by most patients from one to several hours after the injection, and about half the patients will retch and vomit. These symptoms may last for several hours, but in nearly all cases the patient is ready to accept another injection the next day. Vomiting is hazardous in a patient with a haemorrhagic diathesis. Toxic effects on the hæmopoetic system are unavoidable with therapeutically effective doses of the nitrogen mustards. The leucocyte count often falls even before the completion of the 4 injections ; a leucopenia is followed rapidly by a granulocytopenia, so that, within a week or so, the total white cell count may go down to 1000 cells per c.mm. In from 2 to 4 weeks the count usually shows a fair return towards the normal.

As regards the remissions produced by the injections, Craver found them "all too often disappointingly short". The results reported by him are not analysed in detail, but he gives his impressions after an experience of 300 cases. With regard to Hodgkin's disease he believes that the nitrogen mustards will find their best use in generalised Hodgkin's disease with marked constitutional symptoms like fever, night sweats, and itching. X-rays are the best treatment in his opinion for two types of patients : (a) those in whom the disease is confined to one group of lymph nodes, and in whom early aggressive radiation might offer a hope of either cure or very long control (and in some of whom perhaps radical surgery should be employed) ; (b) those cases showing beginning spread, but in whom the disease is still relatively regional and without marked constitutional symptoms.

Lymphosarcoma : 66 cases of this disease were treated (Craver)[5] with rapid but incomplete remission in most cases, and a rapid relapse in the more aggressive forms of the disease. The drug was of distinct value in one case of marked mediastinal involvement with severe dyspnoea. In that patient X-rays might have resulted in a fatality from asphyxia as a result of the usual œdema following therapy.

In 65 cases of leukaemia, the results in general seemed at first to be those produced by X-rays. However, the remissions in chronic leukæmia were of shorter duration (a month or so) and as a rule the differential count was not much altered, unlike the effect of urethane. In the acute leukæmias no great benefit was noted. The effect of the nitrogen mustards on other cancers in the body was disappointing, except in some cases of cancer of the lung in whom remarkable temporary regressions occurred.

Craver summarises his observations at the Memorial Hospital as follows :—

1. None of the nitrogen mustards which have been used so far have given any indication of being able to cure any of the types of cancer treated.

2. Palliative results of nitrogen mustard therapy have nevertheless been marked, and its use may be recommended in (a) Hodgkin's disease with marked constitutional symptoms, (b) advanced lymphosarcoma in which some part of the disease is immediately threatening to life and not amenable to safe extirpation or irradiation, (c) anaplastic carcinomas of the lung.

3. In early and intermediate stages of Hodgkin's disease and in most cases of chronic leukaemia, it seems doubtful whether the drug offers any advantage (in general) over other methods of treatment.

4. Since only a few of the hundreds of possible nitrogen compounds of the mustards have been extensively tried clinically, it may be that other compounds will be found that may be, at the same time, less toxic and more effective in a broader range of cancers. Work on these lines is proceeding in the Chemo-therapy Division of the Sloan-Kettering Institute attached to the Memorial Hospital, New York, and several other centres.

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MEDICAL PRACTICE

IMPLANTATION OF HORMONES

A. P. Pillay

DEVELOPMENT OF IMPLANTATION THERAPY.

Though implantation therapy has been rationalized and made scientific only in comparatively recent years, the principle of its effectiveness was recognised from even as early as 1870, when Hunter discovered that transplantation of testicular tissue caused increase of sex power. In 1849, Berthold noticed that the implantation of cock's testes caused growth of the atrophic capon-comb. The pioneer research worker in this field was Brown-Sequard who, at the age of seventy-two, claimed to have rejuvenated himself physically and mentally by injecting himself with extract of dog's testicles. He "experienced a remarkable increase of strength and endurance and of his mental capacity, as well as, an equally striking improvement in the functions of micturition and defaecation." Other investigators failed to get the results claimed by Brown-Sequard, and the subject remained neglected.

In more recent years, Voronoff introduced the method of implantation of the testicles of anthropoid apes for rejuvenating, based on the mistaken idea that the testicles stored a large quantity of hormones. This was in vogue for some years, but now it is never used as it has been proved to be worthless, because testicles, though they continually produce their hormones, yield these up to the blood stream and do not store them, and so contain only minute traces when separated from the ape's body. Later still, Stanley tried injections of the pulp of the testicles of young but sexually mature rams, based on the same fallacious notion as that of Voronoff. This method was, upto recent years, prevalent in U. S. A. and the Continent of Europe. Such experiments were made because there was then no clear idea of the actual composition of hormones or how to assess their potency.

The scientific study of hormones, and in particular of testicular hormone, may be said to have begun in 1930, when Gallagher and Koch devised a quantitative physiological test, the capon-comb test, by which the physiological potency of male hormone products could be tested. This gave an impetus to further investigations. In 1934-1935, Laqueuer succeeded in isolating from urine-extracts a physiologically active hormone, and soon after Ruzieka and Butenandt produced, independently of each other, the same product synthetically from cholesterol. Thus, large quantities of the hormone were available for research purposes and clinical tests. This synthetized male hormone was termed testosterone. Later, its derivatives, testosterone propionate and methyl testosterone, were prepared.

TECHNIQUE OF IMPLANTATIONS

In the beginning, hormones were administered as injections of oily solutions, by innunction, orally and sublingually. In 1937, Deansley and Parkes experimented with implanting the pure hormone into animals. Endocrinologists then began using it on human beings. The implantation was done first with compressed pellets of the pure crystalline hormone, and later with fused cylindrical rods. Now, crystals suspended in aqueous solution are also available. All these are prepared of testosterone, testosterone propionate, oestradiol monobenzoate, progesterone and desoxycortiocosterone acetate.

Various workers recommend the implantation of hormones in different parts of the body, and by different methods. It is proposed, however, to discuss in this paper only the methods followed in my clinic. So far 79 implantations have been done, with a single hormone or combinations of 2 different hormones.

Pellets[1]

There are two ways of implanting pellets: by open operation and subcutaneously.

By open operation:—The site used by Greenblatt and other early workers is the abdominal wall, midway between the umbilicus and pubis. As this meant deep incision in obese patients, the thigh was selected in my clinic. The front of the thigh, midway between the groin and knee, is shaved and sterilized as usual. The anaesthetic used is 1½% procaine solution. A weal is raised in the skin and the tissues down to the sheath of the muscle are infiltrated. A horizontal incision of about 1 or 2 inches, depending on the amount of fat, is made and the muscular sheath visualised. The sheath is now cut and a pocket made on one side of the incision and the pellet or pellets introduced. If more than one pellet is used, separate pockets are made for each, so that the pellets may not touch each other. It is advisable not to keep the pellets directly under the incision. The sheath is then closed with catgut, and the skin and subcutaneous tissues are approximated by silk sutures. A sterile dressing is put on and kept in place by means of elastoplast.

If the patient does not get the dressing wet, as when bathing, the dressing need not be changed often. On the seventh or eight day, the sutures are removed. Though it is not necessary to confine the patient to bed, much walking and straining of the thigh muscles should be avoided the first few days, otherwise the pellets are likely to be extruded. It is not advisable to use pellets of more than 200 mg.

No. of implantations performed		18
Doses used :	Testosterone & Testosterone propionate	100-400 mgs.
	Progesterone	25 mgs.
	Desoxycorticosterone acetate	50 mgs.
No. Extruded		4.

Subcutaneously :—The method described meant an operation, and the mere mention of the word "operation" frightened many patients and the wound often took long to heal. The site for subcutaneous implantation is the lower part of the abdomen, about 2 inches above the pubic hair and 3 inches to the inner side of the iliac crest. A weal is raised in the skin, as in the open method, with 1½% procaine solution, through which a track about 2 inches downwards, medialwards and inwards, is anaesthetized. A vertical incision about ½ inch long is made, the edge picked up with toothed forceps, and with a long pointed dressing forceps, a pocket is made in the subcutaneous tissue about 2 inches away from the site of the incision. With the same forceps, the pellet is pushed into this pocket. Any oozing blood or procaine solution is pressed out and the wound covered with elastoplast.

No. of implantations : 19 ; Doses : Same as in open operation : No. extruded : 7.

Rods.[2]

Implantation of rods is simple. The method was demonstrated to me, while in London, by Dr. Charles Dusseau of Harley Street. The site and the direction of the track are the same as those used for subcutaneous implantation of pellets. A small stab incision is made with a tenotome or Bard-Parker No. 11 blade. The incision should just penetrate the skin sufficiently to allow the special trocar and cannula [3], used for the purpose, to be pushed with ease into the subcutaneous tissue along the anaesthetized track. When the trocar and cannula are in place, the former is removed, the rod picked up with a small forceps, dropped into the cannula and pushed in with the trocar. When a number of rods is implanted at the same time, they are deposited away from each other, more or less in a cart-wheel pattern. The wound is then sealed with elastoplast which is left in place for 5 or 6 days.

No. of implantations : 16 ; Doses used : 200 mgs. of Testosterone No. extruded : Nil.

Crystules[4]

Implantation of crystules is really not an implantation but only an injection and, theoretically, should be very simple. It is found not to be so simple, as, unless the correct technique is used, the crystules get stuck in the needle. For this are required a 10 c.c. syringe with side bars, a serum needle or any long hypodermic needle about 2 inches in length, a blunt cannula or needle 15 gauge and a 15 gauge needle of about 1½ inches to 1½ inches with a well-fitting stylet[5]. The same syringe is used for anaesthetizing and implantation.

Though local anaesthesia is really not necessary, it is better to anaesthetize the area as in other methods. The implantation is done from a spot about 2 inches below the iliac crest and 2 inches from the sacrum.

The procedure is as follows:

1. With the patient lying on his side, sterilise and anaesthetize the skin and infiltrate a track of about 2 inches, forwards and downwards, using for the purpose the serum needle.

2. Push in the 15 or 16 gauge needle with the stylet through the weal along the anaesthetized track, and let an assistant support it. It may even be left unsupported if the patient lies well forward.

3. Roll the ampule between the palms of the two hands till the crystules are detached from its sides and are seen floating in the solution. Now shake the ampule, first holding the top and then the bottom, vigorously up and down to displace the crystules remaining above the neck, and then open it. Take about 2 c.c. of the procaine solution in the syringe, using the blunt cannula, draw the solution into it, return part of it (now mixed with the procaine solution) into the ampule, withdraw and repeat the process till no crystules are left in the ampule. If necessary draw into the syringe more procaine solution. Remove the cannula and shake the syringe well and hold it for a while with the needle end pointing downwards to dislodge any crystules adhering to the base of the piston. Remove the stylet from the needle and inject quickly. The needle and syringe are immediately withdrawn, pressure applied for a while over the area, and the hole in the skin sealed with one or two layers of elastoplast. It is advisable to have an extra needle, because, if the first one gets blocked the second can be used. Trying to clean the blocked needle with the stylet is only waste of time and the crystules may again become clogged in the syringe. The injection causes no pain whatever at the time, and later the patient will, at most, feel for a few hours only some heaviness over the area. The crystules should not be injected into the muscle, as then the pain and swelling will be much.

No. of cases:		26
Doses used:	Testosterone propionate & Desoxycorticosterone	100 mg.
	Progesterone	50 mg.
	Oestradiol monobenzoate	10 mg.

ADVANTAGES OF IMPLANTATION OVER OTHER METHODS

1. For the oral and sublingual methods to be effective usually high doses of the hormone are required, at least 4 to 6 times the dose effective as injection.

2. The innunction method is messy and only small amounts of the hormone can be absorbed. It is useful only in infants and young children.

3. As regards injections of oily solutions, most of the hormones contained in them is absorbed within a short period, because of the higher absorption rate. High doses depress spermatogenesis, except in cases of sexual infantilism, and generally are harmful especially when the patient suffers from high blood pressure. Two cases have been reported to me where blood letting had to be done to reduce the high blood pressure produced by injecting 25 mg. doses of Perandren.

In implantation, the question of over-dosage does not arise as the rate of absorption is slow. I gave once to a man aged 62 with 230 systolic pressure, implantation of 200 mg. testosterone with no untoward results. The absorption is continuous, and according to Greenblatt[3] who has wide experience, "the method of implantation of pellets has more nearly approached the endogenous mechanism of hormone secretion in the organism." At the time Greenblatt wrote this, rods and crystules were not available.

Opinions seem to vary as to the rate of absorption of the implants. Bishop and Folley believe that absorption depends on the surface area of the implant. They write: "Since absorption depends upon surface area, and since the area diminishes with absorption, hormonal release from the cast pellets gradually declines, in other words it follows a curve, not a straight line. Hormone absorption from a 100 mg. cylindrical pellet is roughly 1.1 mg. per day, but by 50 days absorption is 33% less. Compared with compressed testosterone pellets, the cast pellets were absorbed faster, but some or all of the difference can perhaps be explained by the latter's greater surface area (12% greater)." I found, on checking up, that the average daily absorption of pellets is about 1 mg. at least for 2 months. 200 mg. pellets extruded 60 days after implantation were found to weigh 59 to 62 mg. less. Kochakian found that in Rockland and Buffalo-Marshmice, a pellet of 11 mg. was absorbed only in 80 to 90 days. Biskind, Escamillo and Lisser found that in eunochoids the absorption was more even up to 2 or 3 mg. daily. They make the instructive statement: " The uniform continuous absorption from such pellets is more efficient than injections of the hormone in oil, so that approximately one-fifth of the dosage is required to obtain similar results." Some workers maintain that the rate of absorption depends also on where the pellets or rods or crystules are placed, if on a very vascular surface the absorption is greater, and if on a site where the blood supply is poor, slower. I cannot subscribe to this view, as pellets extruded after implantation on the thigh muscle and subcutaneously, both showed the same rate of absorption. The rate of absorption will thus depend on the surface area and weight of the implant, and hormonal deficiency of the patient. Though reliable data are not available as regards the rate of absorption of crystules, the consensus of opinion seems to be that it is slower from the pellets than from the rods, and quickest from the crystules.

RELATIVE MERITS OF THE VARIOUS TYPES OF IMPLANTS

The use of pellets, by whichever method they are inserted, involves cutting, and are likely to be extruded. They are, therefore, unsuitable for use in routine dispensary practice. The same holds true for rods, though I have not seen them being extruded. It has to be remembered that any method advocated should be within the capacity of general practitioners, as it is to them that the majority of patients resort to for treatment in the first instance. They will, therefore, find crystule injection as the method of choice; and if the majority of doctors, as is reported, fight shy of it, it is because the crystules, as mentioned above, frequently clog the neeedle when full precautions are not taken.

There are two other important considerations. If we assume that the rate of absorption is about 1 mg. a day, the effects of a 100 mg. implantation should last about 100 days and it would replace 2 to 7 oily injections a week during this period. The former method is, therefore, the cheapest and the most convenient form of hormone therapy, from the patient's point of view.

The general practitioner would seem to be fully persuaded that testosterone and its derivatives are a panacea for all types of "impotence", and prescribes these without enquiring into its nature or causation. High doses of oily injections are harmful and, as was mentioned, implantations can do no damage. Let the general practitioner, then, be conversant with methods which, even if used injudiciously and in unsuitable cases and doses cannot harm the patient!

In another paper I shall make a comparative study of the clinical effects of the various methods of administering sex hormones, and also of a new method being tried in my clinic, *viz.*, that of administering them as rectal suppositories.

I am indebted to Ciba Ltd., Basle, and Ciba Pharma Ltd., Bombay, for keeping a liberal supply of pellets and crystules at my disposal.

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1. Pellets, Supplied by Ciba, Ltd.
2. Rods, Manufactured by Organon Laboratories Ltd.
3. Trocar & Cannula, Manufactured by Allen and Hanburys.
4. Crystules, Supplied by Ciba, Ltd.
5. Special needle & Stylet, Supplied by Bombay Surgical Co.

PNEUMO-PERITONEUM FOLLOWING GASTROSCOPY

A CASE REPORT

P. Raghavan and A. E. De Sa*

The occurrence of pneumoperitoneum following gastroscopy, without demonstrable evidence of gross perforation at operative exploration, is rare enough to make an additional case report of such an event worthwhile. Till January 1949, only five such cases have been reported in the literature; the first was that of Schiff in 1941; later Schindler (1945), Berk (1946), Chamberlin (1947), and more recently, Gilbert, Knight and Dalton (1949) reported a case each.

CASE REPORT

A Hindu male aged 40 years was admitted for dyspeptic symptoms and signs suggestive of peptic ulceration with pyloric stenosis. There was a long standing history of upper abdominal pain with vomiting and distention. Physical examination revealed epigastric distention and active peristalsis passing from left to right. Gastric analysis showed a climbing type of acid curve. Barium meal X-Ray studies revealed pyloric obstruction with much residual fluid and no filling defect.

GASTROSCOPY:—After a preliminary gastric lavage four hours previous to the examination, the patient was given 100 mgms of pethidine with 1 /100 grain of atropine subcutaneously. A 1% solution of percaine was used for local anaesthetization of the pharynx and one c.c was squirted into the oesophagus with the Schindler tube. Lavage with the stomach tube brought out only 15 c.c. of mucoid fluid. Though the patient was apprehensive and rigid, the gastroscope was passed easily. There was a considerable amount of secretion in the stomach; no details could be made out. The instrument was withdrawn, and the patient was asked to sit up and belch as he was restive.

He was unable to belch out the air, complained of faintness and had a convulsive seizure. As the seizure was considered to be a manifestation of percaine intoxication, the patient was given a subcutaneous injection of 3 grs. of sodium phenobarbitol. The convulsions subsided, and the patient was placed in the recumbent position. On regaining consciousness the patient complained of upper abdominal discomfort. The abdomen was uniformly distended and on percussion, obliteration of liver dullness was noticed. Perforation with leakage of air into the peritoneal cavity was suspected. On fluoroscopic screening, a pocket of air under the domes of the diaphragm was observed. This was considered confirmatory of a perforation of the stomach and immediate operation was undertaken.

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Anaesthesia—Intratracheal ether.

Operation. The abdomen was opened by a right paramedian incision. As the peritoneum was incised, air escaped with a hissing sound. The anterior wall of the stomach was carefully examined from the oesophagus to the duodenum, but there was no visible perforation. The scar of a healed ulcer was seen on the anterior aspect of the first part of the duodenum. There were emphysematous blebs between the two layers of the lesser omentum. The stomach was not mobilized for inspection of its posterior wall; a posterior no-loop gastro jejunostomy was performed.

The abdomen was closed in layers with chromic catgut, and the skin with interrupted linen sutures. The patient made an uneventful recovery, and was discharged twelve days after operation.

DISCUSSION

Interest in the condition centres round the method by which air escapes into the peritoneal cavity—and in view of the fact that the management of the condition, if diagnosed with certainty, is conservative, it becomes important to define a set of symptoms and signs on which the diagnosis can firmly rest.

Schindler believed that seepage occurred through a tiny tear in the stomach wall, which seals over and is not demonstrable at operation. Chamberlin attributes leakage to escape of air through the base of an ulcer and notes, among the signs that have been consistently observed after the catastrophe, inability to inflate the stomach and gastric distension. There is no other evidence of perforation except the presence of free air in the peritoneum, though Berk has described severe abdominal pain as occurring in his patient, and Chamberlin's patient developed fever and leucocytosis within twelve hours. Inability to belch air has been described by Chamberlin and by Gilbert, *et al.* as a pathognomonic symptom of the condition. Subcutaneous emphysema was noted in his case by Chamberlin.

This report would represent the earliest exploratory operation on a case of pneumoperitoneum following gastroscopy—exploration having been undertaken within one hour of the accident. The earliest period at which operation has been undertaken in the literature we have had access to, is three hours in the case described by Schindler.[5]

Looking back on the case here reported, we feel that the seepage of air from the stomach occurred during the tonic phase of the convulsive seizure, which we are inclined to regard as a manifestation of percaine sensitivity.

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CURRENT MEDICAL LITERATURE

MEDICINE

THE Q3 AND QS3 DEFLECTIONS IN THE ELECTROCARDIOGRAM; CRITERIA AND SIGNIFICANCE. HARRY E. UNGERLEIDER, AND RICHARD GUBNER, M.D., American Heart Journal. 33: 807-818, 1947.

Harry E. Ungerleider and Richard Gubner report a group of a total of 1355 subjects, in all of whom the history, physical examination, and teleroentgenogram were reviewed in addition to the electrocardiogram.

This analysis was undertaken to establish criteria of abnormality of the Q3 deflection in the electrocardiogram. Certain findings appear to aid in the differentiation of the "normal" Q3 and the Q3 due to coronary disease. The findings which follow were found to be present in 10 per cent or less of normal individuals with a Q3 wave conforming to Pardee's criterion. They were present at least three times as frequently in subjects with a Q3 due to coronary disease.

(*a*) Weight less than 5 per cent overweight.
(*b*) Absence of S wave in Lead I.
(*c*) Q wave exceeding 1 mm. in Lead II.
(*d*) Low T wave in Lead II (less than 1 mm.).
(*e*) Wide Q wave in Lead III (0.04 second or more in duration).
(*f*) Q wave in Lead III which equals or exceeds 75 per cent of the amplitude of the tallest R in the limb leads.
(*g*) Deep inversion of the T wave in Lead III (exceeding 2.5 mm.).

In order of importance the features which were most significant of an abnormal Q3 were found to be a low T wave in Lead II, the presence of a Q in Lead II which exceeded 1 mm. in amplitude, and an absence of an S wave in Lead I. Employing the six electrocardiographic criteria (b-g), it was found that 94 per cent of patients with a Q wave in Lead III due to coronary artery disease exhibited one or more of these abnormalities, while only 24 per cent of normal subjects with a Q3 conforming to Pardee's criterion showed one or more of these findings. The presence of one or more of these abnormalities in the standard limb leads offers a satisfactory means of distinguishing the so-called normal from the pathologic Q wave in Lead III.

Absence of the S wave in Lead I not only confers added significance to a Q3 a deflection, but may be of some significance without relation to its association with a Q3 deflection. It appears to be associated with left ventricular enlargement since it was present in fully two-thirds of the patients with advanced hypertension who exhibited left axis deviation. The occurrence of this finding in 18 per cent of normal individuals with left axis deviation indicates that absence of S1 is not a sufficiently specific abnormality to be of diagnostic value of itself. While not specific, it is by far the most frequent electrocardiographic variant accompanying left axis deviation in left ventricular hypertrophy, since an absent S in Lead I occurred twice as often as any other electrocadiographic abnormality. The QS3 pattern is closely related to the Q3 pattern and is, in effect, equivalent to a Q3 plus an absent Si. Small Q waves in Lead III, not conforming in amplitude to Pardee's criterion, are not significant unless there is also an absence of the S wave in Lead I.

A limited mortality study suggests strongly that the Q3 deflection is a significant abnormality which should not be dismissed simply because of associated overweight and transverse position of the heart. Fifteen of seventeen cases with no cardiovascular abnormalities other than a Q3 deflection died of heart disease, after an average survival period for the entire seventeen cases of 5.7 years. The duration of life was shortest (4.4 years) in a group of five cases in which the Q3 pattern was accompanied by electrocardiographic findings which are indicated by this study to increase the significance of the Q3 deflection.

A. KARMALLY.

THE CLINICAL USE OF ANTICOAGULANTS J. PHARMACY & PHARMACOLOGY I, 353-366, June 1949 117 refs. AUTHOR'S SUMMARY.

The utility of a non-toxic anticoagulant in the therapy and prophylaxis of thrombosis in man has long appeared probable, and was confirmed as soon as purified heparin became available in quantity. The first favourable clinical reports from Stockholm and Toronto have been followed by some hundreds of papers describing the successful use of both heparin and dicoumarol in a variety of thrombo-embolic conditions. It is impossible to give a brief adequate summary of this work; an excellent account will be found in the monograph by Jorpes who seems, however, to emphasise unduly the toxic action of dicoumarol on the liver. Both drugs appear to have an established place in therapy. As compared with heparin, dicoumarol has the advantages of cheapness and of effectiveness on oral administration: its drawbacks are its slow onset of action, which makes it useless in emergencies unless supplemented by heparin, and the considerable variability in the response of individual patients. All anticoagulant therapy involves the risk of haemorrhage, and this risk can only be minimised by close supervision of the patient and frequent checks of clotting time (in the case of heparin) or prothrombin time (in the case of dicoumarol).

The numerically most important field of usefulness for these drugs has been the prevention and treatment of post-operative thrombosis, particularly after pelvic operations. The incidence of this complication is notoriously variable, and the availability of an effective therapy should not distract attention from the importance of simpler measures, especially active and passive movement of the limbs. Treatment is usually begun on the second day, when the risk of bleeding at the site of operation is small, and continued till the patient is ambulant. Opinions vary as to whether anticoagulant therapy should be used routinely after pelvic and abdominal surgery or reserved until signs of clot formation appear. Early diagnosis of latent thrombosis is naturally of the greatest importance, and phlebography of the lower extremities and tests revealing hypercoagulability of the blood, such as the heparin tolerance test of the Takats have been found useful for this purpose.

Other forms of active venous thrombosis respond equally well to anticoagulant therapy, which undoubtedly reduces the incidence of embolic complications. Thrombosis of the mesenteric veins, the retinal veins and the cavernous sinus, have all been treated successfully, in addition to the more common condition in which the initial site of clot formation is one of the deep veins of the lower leg. The status of the anticoagulant drugs in the treatment of occlusive coronary artery disease is still uncertain. They are quite useless in subacute bacterial endocarditis. Overdosage with heparin is treated by withdrawal of the drug, when the blood regains its normal clotting power within a few hours, or in emergency by the intravenous injection of protamine, which has an instantaneous effect. Dicoumarol overdosage can be corrected by the administration of massive doses of vitamin K preparations, or more rapidly by the transfusion of fresh blood or plasma.

Finally it should be mentioned that heparin is a valuable adjunct to vascular surgery, and has some advantages over citrate as an anticoagulant in blood ransfusion.

The expense and inconvenience of heparin therapy have undoubtedly restricted its field of usefulness. While intravenous administration, either several times a day or by continuous drip, is still the method most commonly used, a number of menstrua for the incorporation of heparin have been devised which permit a prolonged effect to be obtained with a smaller number of intramuscular or subcutaneous injections.

J. C. PATEL.

THE TREATMENT OF AMOEBIC LIVER ABSCESS WITH CHLOROQUINE—SIR PHILIP MANSON-BAHR—Jour. of Trop. Med. and Hygiene 52; 91-93, 1949.

The author states that in chloroquine " we possess a drug which by concentration in the liver parenchyma acts upon E. histolytica in this situation." It is ineffective in intestinal infection with the same organism. The author gives an account of 28 intestinal and 6 hepatic cases treated. 13 of the former continued to show E. histolytica in stools after one course of chloroquine; in 6 hepatic cases symptoms disappeared abruptly within a few days and did not recur during follow up periods ot two or twelve months.

P. V. GHARPURE.

ELECTROLYTE CHANGES IN NEPHROSIS. BY CHARLES L. FOX—DONOVAN J. McCUNE. The American Journal of the Medical Sciences. 216: 1-10, 1948. Tables 2—Fig. 4—Ref. 30.

The authors report the electrolyte changes in plasma, extracellular fluids and urine in nephrosis and nephrotic stage of nephritis. The plasma sodium and bicarbonate falls and there is increase in chlorides. This change is reflected in urine by low excretion of sodium and acid reaction. There is increased excretion of potassium. The cause of such a change is at present unknown. The fall in sodium and acidosis in plasma and extracellular fluid will induce the shift of fluid from the extracellular to intracellular compartment. There will be reduction of plasma volume and oliguria. In this manner oedema of nephrosis may be intracellular oedema.

Large doses of sodium and bicarbonate in form of its precursors along with potassium salts were administered to children suffering from nephrosis or nephrotic stage of nephritis. The rise in plasma sodium and reduction of acidosis led to shift of fluids from intracellular to extracellular compartment. After a few days diuresis with composition of urine very similar to plasma representing minimal osmotic work by kidney set in. The study of overall balance sheet indicated that a far larger quantity of chlorides than expected was excreted. The site of such a store of chlorides may be in the tissue cells. Following the diuresis children remained oedema free on the same therapy. Fourteen children have been treated like this and maximum period of observation is 28 months.

Plasma proteins remained virtually unchanged in some cases showing that at least in some cases not the plasma proteins but an electrolyte imbalance was the cause of oedema in nephrosis.

B. B. YODH.

THE TREATMENT OF ANURIA BY INTESTINAL PERFUSION. BY H. M. MARQUIS & F. P. SCHNELL. The American Journal of the Medical Sciences. 215 : 686-693 1948. Fig. 4. Ref. 4.

The authors report a case of anuria following hydrocarbon poisoning. She was comatose and blood N. P. N. was 330 mgm. Two Miller-Abbott tubes were passed—one was kept in duodenum and one in the jejunum and intestinal perfusion was started using intestinal mucus membrane as dialysing membrane, to excrete waste products. The blood N. P. N. fell to 66 mgm. in 24 hours. The blood creatinine level kept on rising slowly. No information was obtained on phenols paracresols indicans etc. At the end of seven days patient was conscious oriented and complained of no discomfort. She developed multiple extra systole and died suddenly on the 15th day.

Miller-Abbott tubes did not give much trouble. Its position was controlled by fluoroscopy. When patient became conscious she tried to vomit it out or pull it out. This was checked by sedatives.

The perfusion was started with 0.1% sodium chloride. Patient developed massive oedema. This was replaced by 10% glucose. Oedema was reduced but patient developed acidosis. This was replaced by 0.8% sodium chloride with 0.1% sodium bicarbonate. The perfusion fluid was altered according to the condition of the patient. Due to lack of facilities frequent studies in blood chemistry, water acid base and electrolyte balance were not done and serum potassium level fell to 1.1 m Eq. per litre. The authors believe that the patient died of ventricular fibrilation due to low serum potassium. This method has great possibilities provided frequent studies in blood chemistry are made and balanced perfusion fluids are employed.

S. N. SHAH.

MIXED INFECTION IN SUBACUTE BACTERIAL ENDOCARDITIS. BY MERVIN G. OLINGER. Arch. of Int. Med.—81 : 334-341, 1948 1948. Fig. 3 Ref. Nil.

Mixed infection in subacute bacterial endocarditis, though known, is a rare occurrence. Prior to advent of antibiotics, it was of merely academic interest but today, it materially alters the outlook of a case.

The author reports two cases. In one case C. pseudo-diphthericum was found along with Str. viridans. The patient did not respond well to 400,000 units of penicillin per day, but when the dose was doubled, there was improvement at once. This was explained by comparative resistance of C. pseudo-diphthericum.

In another case H. Influenzae were found along with Str. viridans. Treatment with 24,00,000 units of penicillin per day failed to produce amelioration. So 4 gms of Streptomycin were given along with penicillin for 10 days. Temperature responded, and after a stormy course, the patient recovered.

The recognition of a mixed infection has great therapeutic significance.

S. N. SHAH.

A COMPARATIVE EVALUATION OF TETRAETHYLAMMONIUM CHLORIDE AND SODIUM AMYTAL IN PATIENTS WITH HYPERTENSIVE CARDIOVASCULAR DISEASE. By IRENE G. TAMAGNA—CHARLES A. POINDEXTER. The Am. J. of Med. Sc. 215 651 to 654, 1948, Fig. 3 Ref 11.

The Sodium Amytal test for evaluation of hypertensive subjects is fairly common. While the patient is at rest Sodium amytal is given every hour for three hours in three grain doses and blood pressure is taken every 30 minutes for 4 to 6 hours. Sodium amytal depresses the vasomotor center the hypothalamus, depresses the proprioceptive mechanism regulating vasomotor tone and it dilates the peripheral blood vessels.

Tetraethylammonium chloride blocks transmission of postganglionic nerve impulses at sympathetic ganglia, and thus, blocking vasoconstrictor nerve impulses, produces fall in blood pressure. Its action resembles temporary thoracolumbar sympathectomy. While the patient is at rest, 0.2 mgm. of T. E. A. C. in 2cc. are given intravenously taking 1½ minutes to inject; Blood pressure is taken every 30 sec. during the injection and every minute afterwards for half an hour.

The author has performed both the tests in 68 hypertensive subjects; Fall of blood pressure was similar in both the tests. Difference in fall of blood pressure was within 15 mg. in 51 cases. In the case of Sodium amytal the patient is drowsy all the time and it takes about five hours, while in T. E. A. C. test the patient is not drowsy and it takes only half an hour. No serious unfavourable reactions were noted due to sudden fall of blood pressure.

S. N. SHAH.

NEUROCIRCULATORY ASTHENIA, ANXIETY NEUROSIS OR THE EFFORT SYNDROME. BY M. E. COHEN, P. D. WHITE, BOSTON, R. E. JOHNSON. Arch. of Int. Med. 81 : 260-281 1948. Tables 6—Fig. 3—Ref Nil.

Neurocirculatory asthenia has enjoyed a varied terminology without exact limit of any term being well defined. Here this name is adopted for being moderately descriptive and non-committal.

Clinically there is a multitude of symptoms related to cardiovascular respiratory function, limitation of muscular effort and emotional instability. There is paucity of physical signs. All clinical and laboratory findings taken at rest are within normal limits.

From their history, two groups are differentiated. Those patients who enjoyed full health before were called acute cases, and those who never had such a fortune were called chronic cases of neurocirculatory asthenia.

During exertion they show higher pulse and respiratory rates, and poor utilisation of oxygen as compared to normals, and when, and given heavy work to do as long as they can, they fall out earlier than controls. These findings are consistent with the hypothesis that neurocirculatory asthenia is an abnormality of aerobic metabolism. For the same amount of work they produce greater amount of lactic acid than normal.

Their pain perception threshold is normal but pain reaction threshold is lower, They have normal intelligence quotient, but they fall in the psychoneurosis group.

Their family history shows higher incidence of neurocirculatory asthenia in their blood relations.

The etiology and pathology and the factors which precipitate and aggravate the disease are unknown.

The follow up studies revealed that discharge from the army does not immediately cure the disorder. Most of them went on suffering off and on.

The authors conclude that neurocirculatory asthenia is a definite disorder of aerobic metabolism and not malingering.

S. N. SHAH.

TENTATIVE APPRAISAL OF VITAMIN B12 AS A THERAPEUTIC AGENT—SPIES, T. W.; SUAREZ, R. M. AND OTHERS. J. A. M. A.—139: 521-525, 1949—one table and three graphs.

The authors report their observations on the effect of Vitamin B12 in macrocytic hyperchromic anaemia. The drug was tried only in macrocytic hyperchromic anaemia with red blood cell count below 2.5 million per cmm., colour index of 1.0 or more, and with megaloblastic arrest of sternal bone marrow. 21 such patients and fourteen pernicious anaemia patients with subacute combined degerneration were given this drug. In each case the administration of Vit. B12 was followed by good clinical improvement. Between 3 and 5 days of commencement the patients felt better, appetite improved, and soreness of tongue disappeared. In cases of sprue stools volume decreased by 6th day. In 14 cases of pernicious anaemia, with mild or severe subacute combined degeneration, the effect was remarkable. Within 92 weeks of the administration of Vitamin B12, dramatic improvement in relation to features of peripheral nerve and posterior column involvement, was noted. Vitamin B12 is the most effective antianaemic substance known. It is the only pure chemical substance known to be effective in relieving subacute combined degeneration. The dosage of Vitamin B12 varies greatly from patient to patient. Most patients seem to respond minimally to, from 8 to 10 micrograms while perhaps the average patient will respond maximally to 100 micrograms Vitamin B 12 has no effect on leukopenia of infections, idiopathic purpura, secondary anaemias, aplastic anaemia or leukaemia.

K. U. JHATAKIA.

INTRAVENOUS USE OF FLUIDS IN BRONCHIAL ASTHMA. JOHN M. SHELDON—J. A. M. A. 139: 506-07 1949.

The author discusses the use of electrolytes in the treatment of asthma. Schaer first tried in 1927, small doses of hypertomic solutions of dextrose intravenously in bronchial asthma with good results. Later on Lepak in 1934 reported favourably of concentrated dextrose solution given intravenously in asthma. The benefit from intravenous use of dextrose may come through the hydration it gives to the patient. It is now generally felt that patients with status asthmaticus should be kept in well hydrated condition. Various types of fluids have been tried in the past. Hypertonic sucrose solution produces renal damage and should not be used. Calcium is generally regarded useless. The only electrolyte which has been found useful is dextrose.

Dextrose in 5% strength in distilled water has been advocated. Such solutions are isotonic and will supply both the water and calories. The quantity to be given depends on the degree of dehydration of the patient but in general it need not be more than 3000 cc. in 24 hours. It is superior to isotonic saline as saline often makes asthma worse.

Contraindications to the intravenous use of dextrose are few, and among these, a weak myocardium must be noted as the chief one.

K. U. JHATAKIA.

AUREOMYSIN IN TYPHUS AND BRUCELLOCIS. KNIGHT, RUIZ-SANCHEZ AND McDERMOTH, Am. J. Medicine, 6, 407 April, 1949.

Eleven patients with typhus, and five with brucellosis were treated with aureomycin. Striking improvement occurred uniformly in the typhus and brucella infections immediately after the start of therapy.

The diagnosis of typhus was established in all the patients by the high agglutiuation titre of the serum for the Weil-Felix reaction, which ranged from 1:640 to 1:3200. Aureomycin was administered orally in divided doses in 100 and 250 mg. capsules. The average dose was 175 to 200 mgs. per Kg. per day in equally divided doses at three-hourly intervals. In every instance the institution of therapy was followed by a remarkable improvement in all of the signs and symptoms of typhus. The change was clearly evident in the first 24 hours. No relapses were noted even 3 to 6 months following treatment.

Five cases of brucellosis were treated, 4 acute and one chronic. The diagnosis was established by demonstration of bacteremia in two cases and by significant rise of antibody titre in the others. One case had meningeal symptoms. The 4 acute cases had been febrile for 9,26,60 and 75 days respectively before treatment. The chronic case had been ill for 2 years. The dosage used was 6 Gm. the first day in divided doses, and subsequently 4 Gm. daily for 5 days. The patient with chronic brucellosis experienced no improvement. In the acute cases the most impressive results was noticed in the patient with meningo-encephalitis who showed dramatic symptomatic improvement in 48 hours and complete recovery in a week The other cases showed marked improvement but two had relapses. A longer total period of therapy is probably advisable.

E. J. BORGES.

SURGERY

THE ASSOCIATION OF CARCINOMA OF THE THYROID GLAND AND EXOPHTHALMIC GOITRE. PEMBERTON AND BLACK, MAYO CLINIC. Surg. Clin. N. Amer. 28 : 935-52, Aug., 1948.

The supposed rarity of association of carcinoma of the thyroid and exophthalmic goitre has been widely accepted. As long as surgery was considered the only effective treatment for exophthalmic goitre this question was only of academic interest. Now that many of these cases are being treated and controlled by anti-thyroid drugs, and there has been some evidence of carcinogenesis with the use of these drugs it becomes necessary to know what the incidence of cancer in exophthalmic goitre has been in the past.

From the records of the Mayo Clinic the following data have been obtained. In 3500 operations for exophthalmic goitre in 15 cases a carcinoma was found in the resected tissue (0.4 per cent.). In 1310 carcinomas of the thyroid gland in 22 cases the malignant lesion had developed in the gland of a patient who had exophthalmic goitre (1.75 per cent.). The finding of a carcinoma in the thyroid gland of a patient who has received anti-thyroid drugs does not necessarily imply an etiological relationship between the drug and the malignant lesion.

E. J. BORGES.

ECCHYMOSIS OF THE ABDOMINAL WALL AS AN EARLY DIAGNOSTIC SIGN OF DISSECTING ANEURYSM OF THE AORTA. BY RAYMOND GREEN & OTTO SAPHIR. The American Journal of the Medical Sciences. Pages 216: 24-26, 1948. Vol. 216 No. 1 Ref. 4.

The authors report a case of a woman aged 50 years who developed pain in the chest then in the abdomen and numbness and inability to move the left leg. The left leg was pale and cold. Femoral pulse was absent and there was loss of sensation. The problem here was whether this was a case of femoral embolism requiring surgical intervention or it was a dissecting aneurysm involving left femoral artery. In one and half hour there appeared a patch of ecchymosis on the left lower abdominal-wall indicating bleeding from left inf. epigastric artery which settled the diagnosis. The presence of anuria in absence of shock and presence of fresh blood in urine indicated involvement of renal and mesenteric arteries. This was confirmed at autopsy.

B. B. YODH.

SUTURE OF PERIPHERAL NERVES. FACTORS AFFECTING PROGNOSIS. KIRKLIN J W ETALIA (Mayo Clinic). SURG. Gynec. Obstet. 88, 719-730, March, 1949.

A careful study has been done of 2,849 patients with 3,276 injuries to peripheral nerves which were admitted to one army installation during 1942 to 1945 Of 957 neurorraphies done only the records of 755 have been analysed as in these there were good records and follow-up notes. The authors summarise the results of their analysis as follows :—

Complete recovery of function, to a degree comparable to the normal state is indeed rare after nerve suture. Eminently satisfactory recoveries, however can be obtained in many instances. The patients interests are best served by accurate end-to-end anastomosis of the nerve within3 months after injury, and preferably in the first month after injury. High lying injuries such as those of the brachial plexus, should be repaired early. However repair is of value even when done as long as 15 months after injury. Low lying injuries recover better after repair than high injuries.

Large gaps between the healthy portions of a divided nerve offer a temptation to the surgeon to deem the lesion inoperable, or to perform brief suture with the hope of subsequent resection and suture. Good results can frequently be obtained in these cases if the surgeon is prepared and willing to undertake an extensive dissection of the nerve in order to make union of healthy ends possible. Despite some encouraging results the superiority of the use of autogenous nerve grafts over end to-end anastomosis of the divided nerve in such situations has not been conclusively demonstrated.

There is no advantage in wrapping the line of suture with tantalum foil. A few metallic sutures at appropriate points in the nerve ends are of value in that they allow the surgeon to assure himself radiographically that the anastomosis is still intact. The surgeon must not be discouraged at any time during operative procedures on peripheral nerves, for it is usually possible to effect a satisfactory neurorraphy.

E. J. BORGES.

TRANSPLANTATION OF ARTERIAL GRAFTS—GROSS, R. E., BILL, A. H. AND PEIRCE E. C., Surg. Gynaec Obstet. 88, fl89-701, June, 1949.

The authors describe a method for the preservation of arterial segments for grafting. The vessels to be used are removed from donor animals between 1 and 6 hours after death, and have been kept for periods of as long as 42 days before they were successfully transplanted into other dogs. The method of storage consists in immersing the arterial segments in a mixture of 10 per cent homologous serum in a balanced salt solution to which are added a buffer, a ptt cold indicator streptomycin and penicillin. The flasks are stored in a refrigerator at 1 to 4 degrees centigrade.

As a result of these experimental observations the method was adopted in human cases. Segments of large arteries, or aorta, were accumulated from human subjects who had died in automobile accidents. The body was always opened under aseptic conditions. In eight cases these grafts were used in patients who had a cyanotic type of congenital heart disease, and in whom it was desirable to make some sort of a shunt of blood from the aorta or one of its branches into the pulmonary artery Ordinarily it is possible to bring such vessels together for a direct anastomosis by the Blalock technique (subclavian to pulmonary artery); but under some circumstances it is very difficult to do this because of tension on the suture lines. Therefore the grafts were only used in the occasional case. In this eight cases theree wer two post operative deaths but in both these the grafts wer intact and free from thrombosis.

In one case of a 7 year old boy with coarctation of the arota, 1.5 cm below the left subclavian artery, the narrowed portion was excised, and it was found that the remaining ends could be brought together only with great tension. A graft was therefore inserted from an aorta removed from a human 28 days previously. It measured 5 cm. in length. The patient had an uninterrupted convalescene, and following the operation there was an excellent pulsation in the arteries of the legs The patient is well.

E. J BORGES.

PEDIATRICS

A propos de la vaccination anti-diphterique : Son efficacite G. RAMON. La Presse Medicale No. 43, 612. 2nd July, 1949.

La Vaccination antidiphterique est-elle efficace? ROBERT RENDU. La Presse Medicale No. 43, p. 613, 2nd July, 1949.

Ramon reviews the progress in the decline of incidence of and mortality due to diphtheria since the introduction of antidiphtheric vaccination. He uses reports from Scotland, England, United States of America, Canada, Denmark to demonstrate the benefits of this vaccination. In Scotland, in 1941-42, there were 17,091 cases with 794 deaths in the non-vaccinated but only 2833 cases and 13 deaths amongst the vaccinated. After the launching of a vigorous campaign in England, the number of cases reported in that country fell from 50,797 with 2,641 deaths in 1941 to 18,248 with 472 deaths. In Canada, during a period of three years from January 1943 to December 1945, 38,188 children aged 0 to 9 years were vaccinated. The morbidity rate amongst them was 1.8 per 100,000 against 136 amongst the non-vaccinated. In New York vaccination lowered the mortality rate and only 6 deaths were reported in 1948.

On the contrary Rendu is of opinion that vaccination is not responsible for the improvement; there has been a general decline in morbidity with an improvement in the standard of life and that epidemics have occurred inspite of vaccination. Yet inspite of this, Ramon's discovery of vaccination is now used by all pediatricians as a preventive measure.

G. COELHO.

LEPROSY

Chemo therapy of leprosy—G. H. FAGET AND PAUL T. ERICKSON: J. A. M. A. pp. 451-456. Feb. 14th 1948.

In the past the treatment of leprosy has been thoroughly unsatisfactory. Lepromations or "L"-type was obstinate to any line of treatment and whatever clinical improvement was seen was of very short duration. Nemal or "N" type required treatment of long duration and the results though good were not satisfactory. By proper treatment one could expect to *arrest* the course of the disease but not *cure* it; but even then one had to bear in mind the *quiescent*, periods in the course of the disease to evaluate the effect of the treatment to arrest the disease. Chaulmoogra oil and its derivatives have been discarded in many countries, though not in India. (We still try to cling to the hoary past). Diptheria toxoid and Quinacrine hydrochloride have not been of real use, though they do show improvement in clinical signs and symptoms.

With the advent of sulphne drugs, there is a decided improvement in treatment of leprosy. We are as if on the threshhold of *curing* leprosy. Time alone will prove it. Sulfone drugs, so far used, are. "Promin"—the sodium salt of p.p.'—dieminodiphenly Sulfone—N-N.'—didextrose sulfonate, 'Diasone'—desodium formaldehyde sulfoxylate diaminodiphenyl mefone and "Promisole"—a 4, 2' diaminophergl—5'—thiarolylmlfone. Diaminodipheny mlfone, the patent chemical from which these drugs are derived seems to be the active principle of each.

Technic of administration :—

Promin—an initial dose of 1 gm. is given intravenously. The dose is slowly increased till a maximum dose of 5 grm. daily is given. The injections are given daily for two weeks and discontinued for one week. Definite improvement is seen after treatment of six months. The treatment must be continued for at least three years. During the week of rest, iron and liver may be administered if necessary. Urine analysis and total count of red and white blood cells and estimation of hæmoglobin are done at least every five weeks to detect early manifestation of toxicity. Diminishing number of red cells or white cells are important signs of toxic manifestation. Nausea, vomiting, headache, allergic dermatitis and frequent sneezing are often seen. Hæmaturia is occasionally seen 'Diasone'—is given orally. Treatment is started with 0.3 gm. capsule or tablet by mouth daily. Provided no toxic reactions are observed in two weeks, the dose is increased to two 0.3 gm. capsules or tablets a day. After a few more weeks, most of the patients can tolerate the optimal dose of 0.3 gm. three times a day. Rest periods of two weeks are given every two months. Periodic laboratory examination of blood and urine are done as with patients taking 'Promin.' Iron and liver may be given to counteract secondary anæmia.' Promisole'—This drug is administered by mouth in tablets or capsules containing 0.5 gm. each. At first 0.5 to 1 gm. is given three times a day. After one or two weeks this dose is increased gradually, if tolerated, to an optimal dose of 6-8 gm. per day. Toxic manifestations are similar to to those of 'Promin' and 'Diasone therapy. Laboratory tests are done similarly to guide the dosage. Definite improvement is seen after six months and then it is progressive with no signs of relapse. The treatment must be continued for at least three years. Among the antibiotios Penicillin does not influence the course of the disease. Strepomycin has been found too toxic to continue for a long time and M. Lepræ have been found to become resistent to the drug after some time.

Conclusions.—In chemotherapy of leprosy with 'sulfone' drugs—'Promin 'Diadone' & promisole, improvement in clinical signs and symptoms and more important in histo-pathological picture is sustained and progressive, however slow these changes may be.

PATHOLOGY

DIFFUSE INTERSTITIAL MYOCARDITIS IN CHILDREN—HOUSE, REGINALD K. Am. J. of Path. A.24; 1235-1258, 1948.

The author describes this condition as " a non-specific inflammatory reaction of uncertain etiology. " It is rarely diagnosed clinically and in most cases the findings are obtained after microscopic examination. Clinically there is a progressive myocardial failure, tachycardia, cardiac enlargement, cyanosis and low B. P. The course tends to be rapid and death may be sudden. A granulomatous myocarditis appears to be distinct from different varieties of myocarditis met with. Autopsy shows generally a picture of congestive cardiac failure. The heart muscle is infiltrated with lymphocytes, mononuclear cells, polymorphs, eosinophils and plasma cells, without involvement of the pericardium or endocardium. Four cases have been described in the article with clinical and autopsy findings.

A multiplicity of causal agents has been suggested—tuberculosis and syphilis may be the cause in granulomatous myocarditis. Blastomycosis has been suggested as also Pasteurella tularensis.

In the diffuse interstitial forms the following causal agents are suggested by the author—upper respiratory infections, toxaemias, influenza and other infections,

P. V. GHARPURE.

THROMBOTIC AORTIC OCCLUSION. GEORGE S. STRASSMANN. Am. J. of Path. 24, 1289-1296, 1948.

This article refers to autopsy findings in cases occuring among mentally sick patients. The author gives an account of 382 autopsies in four years work. The cases showing thrombosis in the aorta are grouped thus—(1) with small thrombi (2) thrombi with aortic aneurysm (3) large aortic thrombi which obliterated the lumen of the aorta. The general features of each group have been described. The author states that obliterating aortic thrombi have been observed at every age even in infants. The diagnosis has been made during life and recently several cases have been treated surgically. The obliterating type is more frequent in persons of advanced age. Of 382 autopsies 57 showed aortic thrombi with 13 obliterating the lumen.

P. V. GHARPURE.

DIFFERENTIAL DIAGNOSIS OF RHEUMATOID ARTHRITIS BY BIOPSY OF MUSCLE. GABRIEL STEINER AND J. L. CHASON. Am. J. Clin. Path. 18, 931-939.

The authors describe diagnostic nodular lesions in muscle. 27 cases of rheumatoid arthritis in 126 cases, controls consisting of 12 normal, 70 arteriosclerotic, 6 poly-arthritis and the remainder of cases having skeletal muscle involvement. In 32% of the controls and 96.3% of the cases of rheumatoid arthritis lesions in mucles were seen. They consisted of nodular, cellular infiltrations. In the histological preparations of rheumatoid arthritis the lesions were sharp, nodular, lymphocytic and plasma cell type. They were endo and peri mycelial. The stroma was scanty.

P. V. GHARPURE.

EMBOLISM & THROMBOSIS IN CORONARY DISEASE. BY ALVIN G. FOORD. The Journal of the American Medical Association 138 : 1009-1012, 1948.

Fig. 1—Tables 5—Ref. Nil.

In this article an analysis of 3900 autopsies performed in a small private hospital is reviewed. Excluding 727 new born infants there were 3173 cases above that age. Among these there were 631 cases whose death could be atributed to coronary arteriosclerotic heart disease. These cases can be divided into four groups Group A of 315 cases of recent fatal coronary heart disease. It includes 223 cases of recent infarction with thrombosis, 41 cases of recent infarction without any demonstrable thrombosis, 51 cases of recent thrombosis but death occuring before any changes of infarction could occur. Group B of 107 cases with old infarct and death due to cardiac decompensation. Group C of 34 cases with no infarcts old or new but still dying of cardiac decompensation and Group D of 175 cases with advanced coronary arterio sclerotic disease but dying due to some unrelated condition.

Mural thrombosis was present in 180 cases out of 422 cases with recent or old infarction. Embolic lesions were noted in 25% of cases. Majority of emboli were found in lungs.

B. B. YODH.

CICATRIZING ENTERITIS. (REGIONAL ILEITIS) AS A PATHOLOGIC ENTITY. Current Comment Page 1044 in The Journal of the American Medical Association. 138, No. 14, of Dec. 4, 1948.

The term regional ileitis was used by Crohn and others because the terminal part of ileum is most often first affected, but cecum, appendix, ileum, jejunum, and colon may be involved and hence the term regional is rather inappropriate. Microscopically there is proliferation of lymphatic endothelium, obstruction of lymphatics, oedema, granulomatous lesions with multinucleated giant cells. Later, there is chronic inflammatory change leading to fibrosis. Gross lesions are sharply demarcated area of oedema and induration of intestine and its mesentary and enlargement of its lymph nodes. Late fibrosis and muscular hyperplasia developes in the affected portion.

B. B. YODH.

NOTICE.

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CHLOROMYCETIN IN TYPHOID FEVER

A PRELIMINARY REPORT

R. V. Sathe*

The widespread prevalence of Enteric Fever Infection in this country, its endemicity in many towns and villages with epidemic waves, the associated high mortality, the considerable invalidism following the infection and the considerable economic strain brought by it on the average family are factors which disquieten the practising physician daily. No drug has been found effective against this infection, and Enteric Fever has been described as a disease for the nurses. With the advent of chemo-therapeutics of the Sulpha group hope was cherished that a drug of this group active against enteric fevers would be found. Sulphathiazole in adequate doses was credited with this effect. With the advent of the antibiotic penicillin this hope was revived. Florey prophesied that penicillin in large doses would successfully attack Bact. typhosum. Evans[4] (1946) was of opinion that penicillin exerted a retarding effect on the growth of B. typhosum *in vitro* and *in vivo*. Combinations of penicillin with sulphathiazole have been credited with good results (Bigger[1], 1946, Mc Sweeney[6], 1946). Streptomycin has claimed greater effect on this infection (Reiman *et al*[8]). In a previous contribution in this Journal, I have recorded my experience with the above drugs, which does not corroborate the claims made for them.

Research in the field of antibiotics however, is going on with rapid strides. Thus Burkholder[3] studied a soil actinomycete recovered during 1947 from a soil sample taken from a mulched field in Venezuela. Ehrlich[3] *et al* obtained from this organism a highly purified crystalline derivative Chloromycetin which proved active against R. *prowazekci*, the semivirus responsible for louse-borne typhus. Smadel[3] showed that in embryonated eggs and in laboratory mice infected with rickettsia and psittacosis virus, chloromycetin was very effective. Smadel[9] *et al.*, then treated a small group of patients suffering from louse-borne typhus, in Mexico, in 1948, with encouraging results. At Kuala Lumpur (Malaya) the drug was tried on cases of Scrub typhus. Among the many cases treated some did not conform to the syndrome of typhus, and some of these turned out, by laboratory tests to be cases of typhoid fever. Since then clinical trials on typhoid cases are being made. Woodward[10] *et al.* have published a preliminary report on ten cases of typhoid treated with chloromycetin. Other reports of cases of typhoid fever treated with this drug have appeared (W. H. Bradley[2], Murgatroyd[7]).

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*From the Jamsetji Jeejeebhoy Hospital and Bhatia General Hospital, Bombay.

Chloromycetin (Chloramphenicol) is a crystalline substance with a considerable amount of chlorine in its molecule.' It has a bitter taste, Its stability in solution is greater than that of penicillin and it can be heated to 100° C for five hours without loss of activity. When given parenterally it causes considerable irritation. But it is absorbed from the gastro-intestinal tract and is extremely active when taken orally. Ley[5] *et al* investigated the fate of the drug in normal men. Within 30 minutes after a single dose of 2 gm. appreciable amounts of the drug could be demonstrated in the blood and urine; at the end of 8 hours detectable amounts were no longer found. About 10% of the drug appeared in the urine; the fate of the rest of the drug is unknown but much of it is metabolised. The drug is not toxic to experimental animals and to men. The drug is active against the Rickettsial infections, viruses of Psittacosis and Lymphogranuloma venereum, and a number of Gram positive and Gram-negative bacteria, particularly Friedlander's Bacillus, Bacterium coli, Salmonella typhi, S. paratyphi, Shigella paradysenterriæ, and Hæmophillus pertussis. It is moderately active against various strains of tubercle bacilli.

Twenty-two cases of typhoid were treated with chloromycetin. Of these 4 died within 48 hours of the commencement of administration of the drug and hence have not been included in this report. In all the cases selected for chloromycetin treatment, diagnosis was made by a positive Widal reaction. In eight of the cases the Salmonella were isolated from blood culture.

Supply of the drug has been irregular and uncertain. The cost of the drug is high. In the beginning, therefore, the use of the drug was restricted to only serious cases. Case No. 1 represents such a case. It is felt that this patient survived only due to chloromycetin. In only one case was the drug started on the 7th day, in one on the 8th day and in another on the 9th day; in all other cases, it was started later. This delay was due to the late arrival of patients under observation and due to time lost in diagnostic procedures. If the drug could be given during the first week, it would shorten the period of typhoid septicæmia and would minimise the intestinal lesions. Complications of hæmorrhage, perforation and peritonitis would thus be avoided; central and peripheral circulatory failure would be less common. A plea is, therefore, made for an early diagnosis by blood culture, and early commencement of the drug treatment.

Dosage of the drug and length of administration are under trial. Parke Davis and Co. who produce the drug, recommend an initial dose of 50 mg. per kg. of body weight followed by 250 mg. (one Kapseal) 2 hourly. Owing to inadequate supplies, an initial dose of one capsule (250 mg.) and then one capsule 2 hourly was given in case No. 8. It has produced just as good results. Yodh[11] in a personal communication confirms similar experience. In this same case, a dose of one capsule (250 mg.) three times a day proved ineffective; a constant two hourly dose seems necessary. It was recommended by the producers that the drug should be continued for a week after the temperature was normal, to prevent relapses. (Cf. case 2.) There is all round tendency to shorten the period. In case 1, it was dropped on the day the temperature touched normal. In most other cases, we gave it in two hourly doses for a day after the subsidence of fever, then 3 hourly on the 2nd day and 4 hourly on the 3rd day and omitted it thereafter. No untoward results have followed such a procedure. In cases No. 1 and 7 the drug was omitted even before pyrexia subsided; yet it lowered the temperature and improved the clinical picture. In case 14 the drug was given for the temperature in a relapse with good results.

The temperature comes down by lysis. in most cases over 3 to 5 days, in step-ladder fashion. (Charts No. 8, 9, 15, 16.) In occasional cases there have been secondary rises in temperature. (Charts No. 1 2, 5, 7.)

The effect on toxæmia is more marked, with a favourable resolution of the state. In many cases, this precedes the effect on temperature. Cases No. 1 and 7 are instances of such response.

Relapse occurred in 2 cases: Case No. 1 and 18. It was mild in both of them.

One patient died, 4 days after commencement of chloromycetin therapy; all other cases recovered.

The drug is not very toxic to man. Yet, some unpleasant symptoms are often produced. The commonest of these is sweating; profuse sweats come on, especially in the initial stages of treatment. Nausea and vomiting occur, especially with the first large dose. Diarrhoea occurs in a number of cases. It should be checked with Kaolin and Bismuth and if necessary, even with opium, and the drug should be continued. Mental depression occurs in a few cases, restlessness in others; in case No. 18, delirium occurred, probably due to chloromycetin. Omission of the drug and sedation with paraldehyde were sufficient to control the same. Stomatitis occured occasionally, as in case 18, and was readily corrected by administration of Vitamin B. Complex.

As the report deals with recent experiences with this new drug, brief summaries of the cases are presented. The temperature charts are also included, as they show the dose of the drug given, the day of disease on which it was given, the period over which it was given, and the effect it produced on the pyrexia.

SUMMARY.

(1) Twenty-two cases of Enteric Fever,—8 diagnosed by isolation of *Salm. typhi* from blood, and the rest by Widal agglutination test, treated with chloromycetin, are reported.

(2) Four died within 48 hours of the commencement of the administration of the drug.

(3) The dosage, beneficial and toxic effects are discussed.

(4) It is felt that further work should be carried out to evaluate the dosage.

CASE REPORTS

Case No. 1

E. P. male, age 24, admitted to a hospital on 2nd May, 1949 with a history of continuous fever for 11 days and cough for 2 days. On exam: tongue furred; throat congested; liver +1 finger; lungs moist rales; purpuric spots on back; B. P. 112/72; rest normal. Two of his sisters suffered from typhoid 2 weeks ago. He himself suffered from paratyphoid 8 months ago.

3rd June 1949 Urine: Alb. thick cloud. Pus cells: 8 to 10 per field; occasional epith. cells. R. B. Cs.: 5.2 m, Hgb., 15.5 gms., C I 0.95; W. B. Cs. 1900 per c mm. P: 89% : L: 11% (Leucopenia with neutrophilia).

4th June 1949: Widal reaction B. typhosus H+1 in 250, O+1 in 50

In view of the seriousness of his condition, he was treated with penicillin 50,000 units 3 hourly for 3 days and then with a combination of 100,000 units of penicillin and 1/4 gm. streptomycin 6 hourly for 4 days. He however, became worse and became stuporose, showed subsultus tendineum, picking at bed-clothes, passed stools and urine in bed and perspired profusely. Chloromycetin, 10 capsules first dose and then one capsule 2 hourly was started on the 19th day. This produced slight lowering of temperature but a marked improvement in the general condition. On the 3rd day he recognised persons and in a day more asked for food. He was given 36 gms. of the drug in 11 days; the drug was omitted on the day his temperature remained normal; after 13 days, he had a relapse of 12 days duration; the relapse was mild and settled down without chloromycetin. This patient has made an excellent recovery; and it appears, chloromycetin alone saved him.

Case No. 2

R. K. male, age 17, was admitted to the hospital on the 6th May 1949 for continuous fever for 5 days, cough and asthma of 15 years' duration. He had suffered from rickets in childhood and had a deformed chest. Excepting bronchitis and emphysema, the findings were normal.

Widal reaction B. typhosus H+1 in 125 B. typhosus O+1 in 50 Blood culture: sterile. R. B. Cs.: 4.1m; Hgb.: 80%. CI: 0.95 W. B. Cs.: 6400; P: 64 %; L: 34%, H: 2.

He was put on chloromycetin on the 7th day of fever and responded well. He, however, had a second rise of temperature, while he was taking chloromycetin 1 capsule 4 hourly; increasing the dose to 1 capsule 2 hourly, the temperature again subsided and remained normal. This was one of the earliest cases treated and chloromycetin was continued for 8 days after the temperature was normal.

Case No. 3

R. P. male, age 7, was admitted on 16th May 1949 with a history of fever for

10 days and diarrhoea for 2 days. Phys. Exam.: Normal. T: 102.4° P: 110; R 32. Widal reaction: B. typhosus 0+1 in 50 R. B. Cs.: 4.04 m; Hgb. 74% CI: 0.9 W. B. Cs.: 5600, P: 61%; L: 37%; H: 2%

Chloromycetin was started on 13th day of fever and gave prompt response.

Case No. 4

K., female, age 22, was admitted on 23rd May 1949 with a history of fever for 18 days; cough for 6 days and diarrhoea; 4 to 5 motions daily for 4 days.

Phys. Exam.: T: 105.4°; P: 140; R: 50; slight tympanitis, markedly toxic; Widal reaction: B. typhosus H+1 in 125. R. B. Cs.: 3.4m; Hgb.: 80%; W. B. Cs.; 6500; P: 61%; L: 37%; H: 2.%

Penicillin 50,000 units 3 hourly and streptomycin 1/4 gm. 6 hourly were given. Chloromycetin 10 capsules were started the same day and were given for 4 days, till her death.

Case No. 5

P. E. S., female, age 26, was admitted to the hospital on 1st June 1949 with a history of continuous fever for 10 days, headache, vomiting for 3 days, dryness of mouth, and two to three foul smelling, liquid stools daily for two days. On examination, she was slightly toxic, tongue dry coated, abdomen smooth, spleen not palpable, lungs few bronchitic signs.

Pulse: 96, B. P.: 92/72, R. B. Cs.: 4.1 million; Hgb.: 9.5 gms.; W. B. Cs.: 5250; Urine—no albumin or sugar. 2nd June 1949: Widal test: B. Typhosu s O+ve 1 in 250 H+ve 1 in 250 Clot culture: B. typhosus isolated.

With routine treatment, the toxæmia improved and the diarrhœa and vomiting ceased; but temperature persisted. Chloromycetin was given on the 16th day and the temperature settled to normal on the 18th day.

Case No. 6

M., A. male, age 18, was admitted to hospital on 8th June 1949 with a history of fever for 7 days; frontal headaches from the beginning; Phys. Exam.: Anæmia, slight toxæmia, tongue: moist, coated; abd.: normal, Chest: few bronchitic signs; Pulse: 92, fair; B. P.: 85/55, R. B. Cs.: 4.1 m. Hgb. 11 gms. W. B. Cs.: 4400 per cu. mm, Widal +ve to O & H antigens in 1 in 250 dilution. Inspite of routine treatment Sulphadiazine, penicillin, vitamins, fluids etc., the toxæmia increased markedly day by day, the pulse rate increased to 130, retention of urine developed for a while. Slight abdominal distension and diarrhœa upto 5 stools a day, also developed, but responded to astringent remedies. Digoxin was necessary to control cardiac failure. From the 12th day of fever patient was in typhoid state and passed urine and stools in bed. Drip-saline was given intravenously, 2 pints a day upto the 20th day. Swallowing was difficult, owing to toxæmia. Chloromycetin was started on the 15th day; 2 gms. stat and 1/4 gm. 2 hourly was given upto a total of 15 Gms. At first the drug had to be given by a rigid nasal tube of a size enough to allow passage of capsules. Upto the 19th day, no improvement was noticed; but on the 20th day the toxæmia was less; on the 21st day the temperature came down to normal with crisis, pulse 100, patient took feeds by mouth. For a week the mental condition was not clear, but cleared up subsequently.

Case No. 7

K. G. N., male, age 40, had fever on 10th June 1949 with headache, especially marked in the evenings, during the 1st two weeks of fever. During the febrile course he had abdominal distension of a severe degree, necessitating flatus tube and carbachol tablets. He also showed congestion of the right lung-base, necessitating use of penicillin. 28th June 1949: Blood Widal B Paratyphosus A+ve 1 in 50 dilution. 3rd July 1949: Blood culture report: B. Para-Typhosus A isolated in culture Chloromycetin, 1/4 gm. 2 hourly was started on 29th June 1949. The temperature

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6. McSweeney, C. J. ; Sulphathiazole and Penicillin in Typhoid Fever.Lancet **2** : 114, 1946.
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11. Yodh, B. B. Personal communication, 1949.

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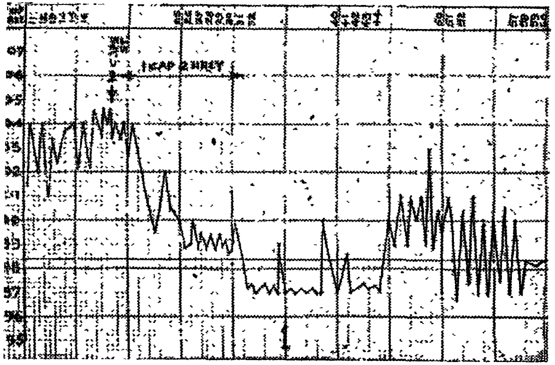

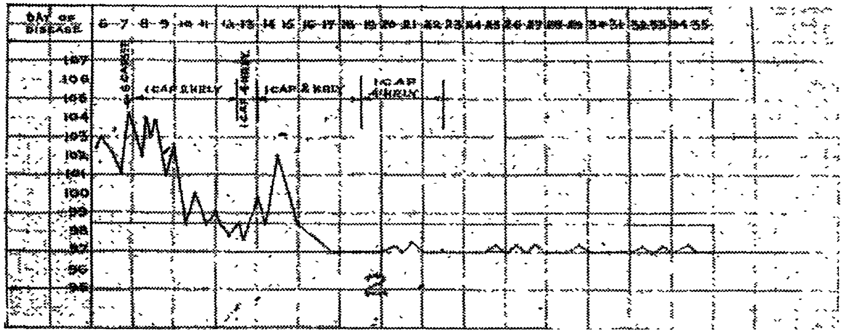

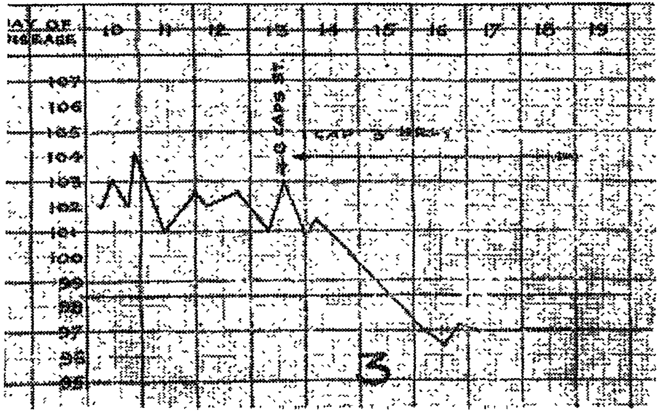

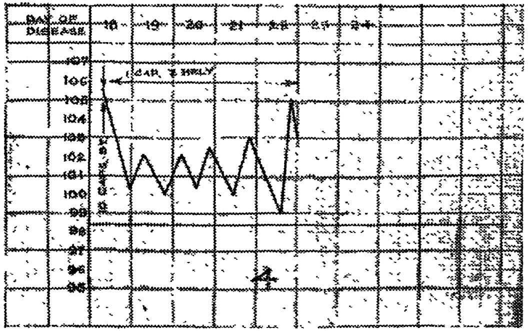

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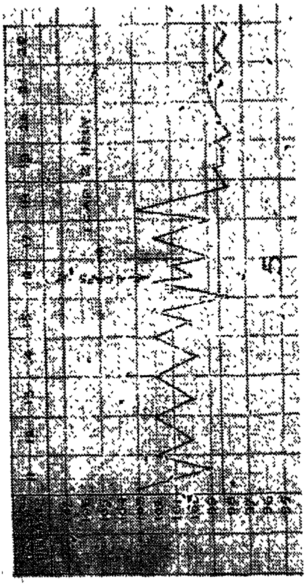

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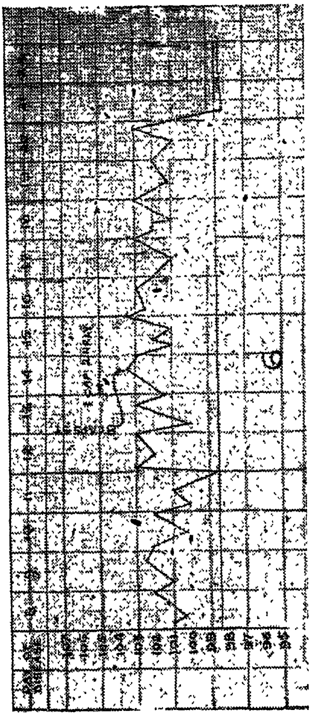

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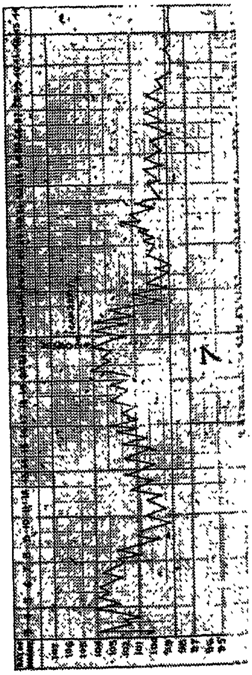

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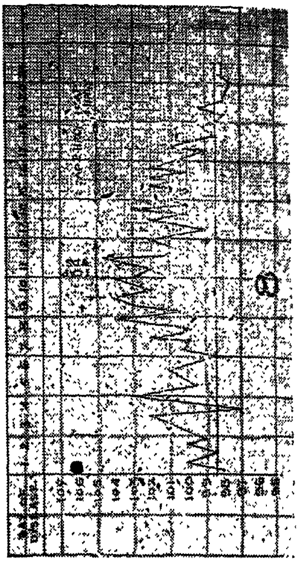

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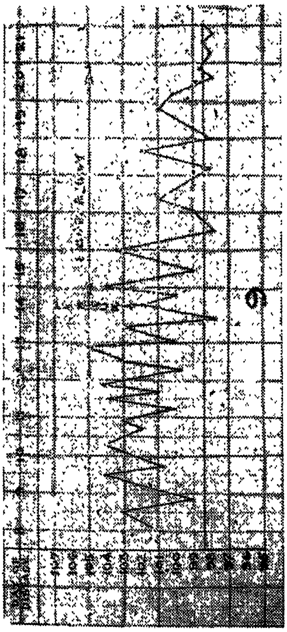
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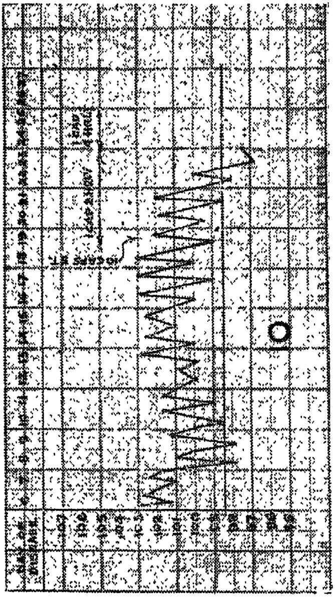
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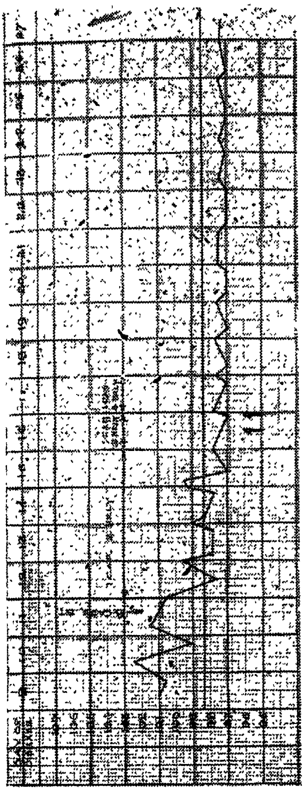
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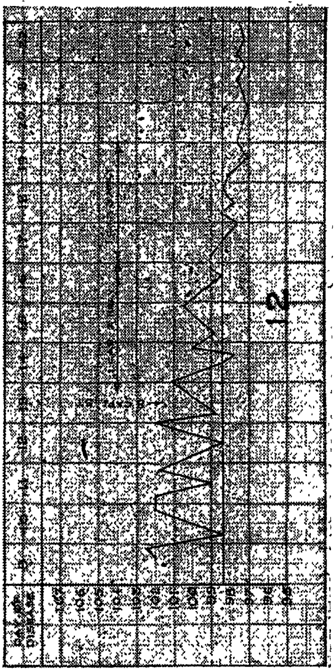
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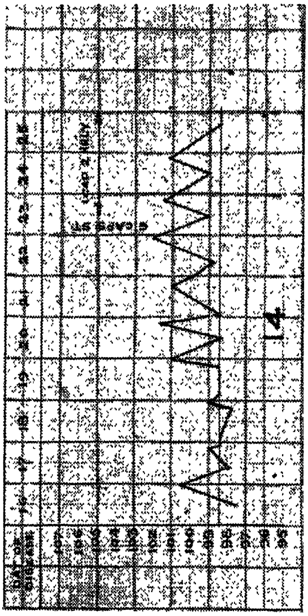

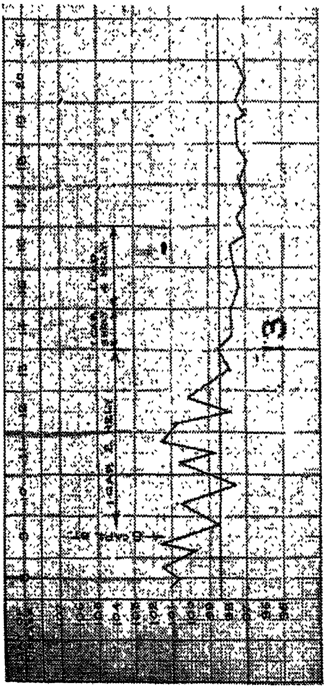

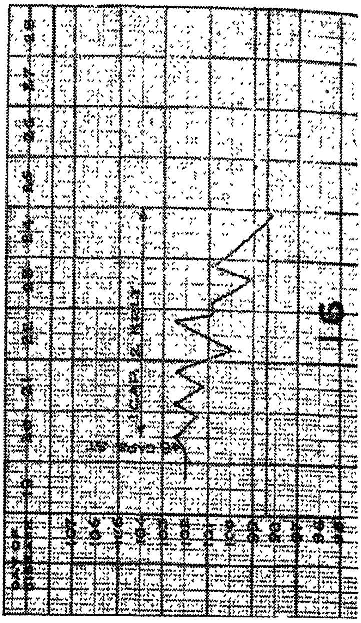

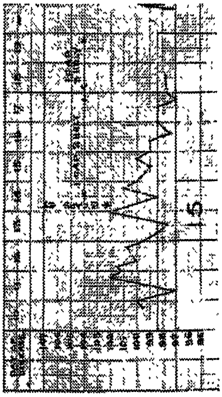

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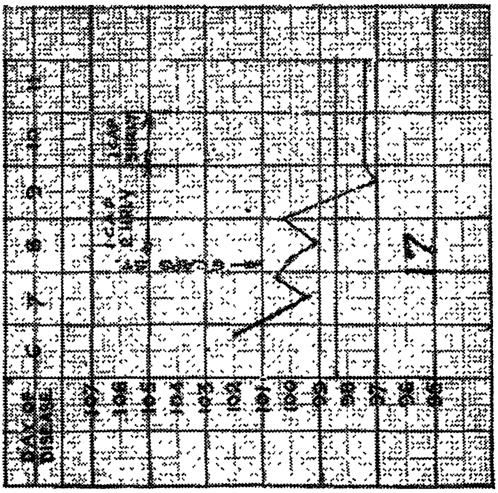

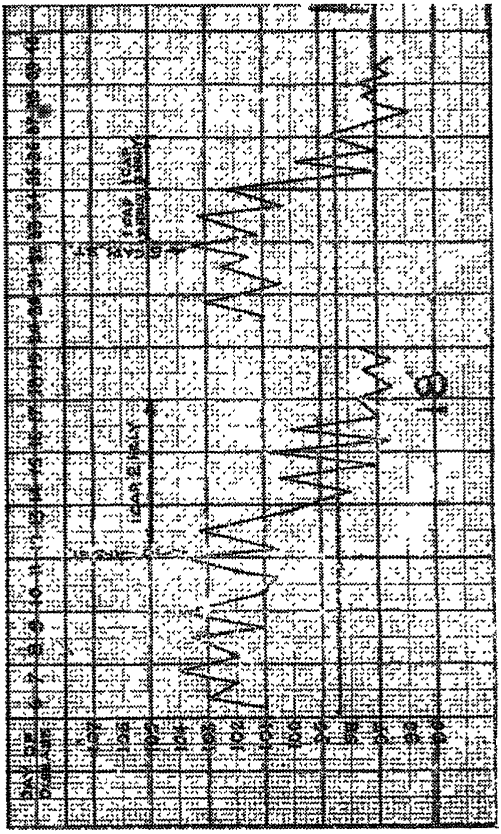

TREATMENT OF TYPHOID FEVER WITH PENICILLIN —SULPHATHIAZOLE AND BACTERIOPHAGE

(A PRELIMINARY REPORT)

J. C. Patel and D. D. Banker*

INTRODUCTION

There is no specific drug in the treatment of typhoid fever. Even streptomycin which held out high hopes has proved disappointing. (Keefer[7] et al. 1946).

In the absence of a specific therapy, good nursing and symptomatic treatment remain the chief mainstay, but three rational ways of treating the infection suggest themselves, *viz.*, Felix 'O' and 'Vi' anti-typhoid serum, specific bacterio-phage and penicillin-sulphathiazole combined as suggested by Bigger[3] (1946).

Ever since the discovery of bacteriophage by d'Herelle, typhoid has been one of the diseases in which this treatment has been given orally by various observers all over the world, but with conflicting results. Heeren and Dilorenzo[6] (1943) observed a shortened period of clinical illness in cases of typhoid fever when specific bacteriophage was employed orally. In India, Banerjee[1] (1939) successfully treated 3 cases of typhoid fever with stock bacteriophage administered intravenously. In these three cases *S. typhi* was isolated from blood before the institution of the treatment.

Recently in America, bacteriophage has been administered intravenously to a singificant number of cases. Bower[4] (1938) used a stock bacteriophage which had a specific lytic action against typhoid bacilli, but not against the particular sub-type isolated from the patient. Spectacular results were obtained in several cases, and this prompted Knouf *et al.* [8] (1946) to employ type specific bacteriophage *i.e.*, one specially prepared against the individual strain isolated from a particular patient. The results of Knouf *et al.*[8] (loc. cit.) were very encouraging; in most cases there was an immediate clinical and bacteriological improvement and the mortality was 5% among the 56 cases treated.

Penicillin alone has been known to be ineffective against the gram-negative bacilli including typhi. Bigger[3] (1946) found that penicillin and sulphathiazole together were bactericidal towards typhi when both the drugs were in high concentration. He suggested that these two drugs might be used therapeutically in typhoid fever. He advocated a concentration of 2 units of penicillin and 10 mg. of sulphathiazole per 100 cc. of serum during the course of treatment. Following this suggestion McSweeney[10] (1946) treated five severe cases of typhoid fever with considerable improvement in all of them.

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* From the King Edward Memorial Hospital, Parel, Bombay.

SELECTION OF CASES

Specific bacteriophage and penicillin-sulphathiazole have been used by us in a series of cases of typhoid fever. Each case was diagnosed on the strength of a positive blood culture, and the treatment was instituted only after isolating the typhi. The majority of cases selected was of a severe nature. The blood, faeces, and urine were cultured at the end of the treatment in each case as a routine.

In the early part of the investigation, treatment with Penicillin-Sulphathiazole alone was carried out, during which period, mild cases were kept as "controls", with the expectation that the next case would be a fairly serious one on which a therapeutic trial would be worthwhile. This resulted in only serious cases being taken up for treatment, and it was soon apparent that an accurate comparison was not possible. It was, therefore, decided to take up every third case in strict rotation for penicillin or phage treatment, or as control, whether the particular case was mild or severe, and this procedure was adhered to, during the subsequent and major period of the investigation. It was considered desirable to have authentic "controls" for assessing the results of treatment, as it is known that there is a variation in the severity and the course of the infection in different places, seasons, epidemics, and persons. The initial irregularity in the keeping of "controls" explains the larger number of cases included in the chart, while the penicillin-treated cases have been a few more than the phage-treated.

During the investigation which extended over a period of one year, *S. typhi* was isolated in blood culture from 60 cases. Of these, 18 were given Penicillin-Sulphathiazole therapy, 14 were treated with bacteriophage, while 18 were left as "controls". The remaining 10 were not taken up for any special treatment nor included as "control" cases, because they were either too mild and had recovered by the time the blood culture report was available, or were admitted in a moribund state and died soon after. The "control" cases were not given any special treatment described later.

BACTERIOPHAGE TREATMENT

The bacteriophage used in the present work was isolated by Dhayagude[5] (1943) from the local sewage. It was found to be specifically active against *S. typhi* in very high dilutions and in the presence of various body fluids. This bacteriophage has been found to be active against all the strains of *S. typhi* isolated so far, but is not specific against any individual strain.

In each case, sensitivity to the protein of bacteriophage was tested by an intradermal injection of 0.1 c.c. of 1 in 10 diluted phage 24 hours before the bacteriophage was administered intravenously. Beyond a slight temporary hyperaemia, none of the 14 cases showed an appreciable reaction.

The dosage and the procedure followed were as advocated by Knouf *et al.*[8] (loc. cit.).

Procedure—The above stock bacteriophage was administered intravenously to 14 cases. In most cases, the quantity was one c.c. of the bacteriophage diluted in 500 cc. of 5% glucose saline which was administered intravenously, by the drip method, during a course of about four hours. The axillary temperature, pulse, and respiration were recorded every 15 minutes during the period of infusion and the following 12 hours. The blood pressure was noted hourly during the period of infusion.

Within approximately two hours of commencement of the infusion, every patient reacted with a rigor. The rigor was fairly severe and lasted usually about 30 minutes, at the end of which the temperature gradually rose upto as much as 106° F (axillary) with a concomitant rise in pulse rate. The respiration became laboured and rapid and many of the patients developed transient cyanosis. The blood pressure was lowered following a preliminary rise.

During this condition, various stimulants like oxygen, nikethamide, desoxycorticosterone were administered where necessary. Blood, urine and faces were cultured in every case 48 hours after treatment. In every case the temperature came down to 97° F. within 12 hours of the therapy with considerable improvement in the general condition but in most of the cases, this improvement was not maintained.

RESULT OF BACTERIOPHAGE TREATMENT

This treatment was carried out in 14 cases, of which one died, the cause of death being associated pneumococcal septicaemia. Of the 13 cases that recovered, seven were in a severely toxic state which improved within 24 hours after the treatment and the temperature dropped to normal within 12 hours. The temperature after remaining normal for 24 to 48 hours rose again, but the course of the fever had been favourably altered. The subsequent cultures of blood, urine and faeces of these patients were negative in four, but positive in three cases. In two of the cases, the temperature came down to normal in the second week within 12 hours after the therapy and after a few slight reactionary rises remained normal (No. 1 and 3). In one of these, the blood culture, taken immediately after the therapy, was still positive though the subsequent urine and stool cultures were negative. In the other case the subsequent blood, urine, and stool cultures were all negative. It must be admitted that the clinical state of these cases before the administration of the phage was not particularly severe. A contact case—husband of No. 3, admitted almost simultaneously, presumably infected with the same strain—was treated as a control and in his case the temperature dragged on for nearly four weeks.

In the remaining four cases the temperature after touching normal rose again on the following day and took more or less its time before settling down. In all these four cases the blood culture remained positive, even after the treatment, though the subsequent urine and stool cultures were negative. The course and height of fever was favourably altered, and recovery occurred without any complications. One of these cases (Case No. 7 in bacteriophage series) was given a course of Penicillin-Sulphathiazole therapy after the second culture had proved positive. The temperature gradually dropped to normal, but the patient suffered relapse during which the blood and urine cultures were positive. The patient finally recovered after a second course of Penicillin-Sulphathiazole.

Among these cases therefore, though the mortality has been low, the rapid fall of the temperature to normal by crisis and accompanying clinical and bacteriological cure have not been observed in our series. The detailed results are presented in Table 1.

TREATMENT WITH PENICILLIN-SULPHATHIAZOLE

Procedure—This treatment was tried out in 18 cases. The dosage adopted in this series was a slight modification of that employed by McSweeney[10] (loc. cit.), but in most cases consisted of only one course. Penicillin 200,000 units dissolved in normal saline was injected by the intramuscular route every two hours till a total dosage of 10 to 12 million units was reached, spread over four to five days. In one case a larger total dosage of penicillin was administered *viz.*, 16 million units over a period of 7 days. Sulphathiazole was administered simultaneously in a dosage starting with 2 gms. followed by 1.5 gms. four hourly, day and night, over the same period, the total dosage of sulphathiazole being usually between 38 to 52 gms. over a period of four to five days. The maximum dosage was 63 gms. in one case, over a period of 7 days.

During the course of the above treatment, routine examinations of the total and differential leucocytic counts were carried out before and after the completion of the treatment. In none of the cases treated with these large doses of sulphathiazole was there any significant decrease in the total count or in the absolute number of the neutrophiles. In point of fact, in some cases, an increase in the total count was observed. We have no definite explanation to offer for this increase, but it is possible that it might be due to a general decrease in the toxic effects of the organisms as reflected in the bone-marrow.

Though a routine examination of urine was done at the time of admission, urinalysis was not carried out in any of these cases during the course of the treatment. None of these cases, however, despite the large doses of sulphathiazole, ever developed any apparent urinary complication, probably because of an insistence on a large fluid intake in every case. The output of urine in every case was above 40 oz. in 24 hours.

As a routine in every case, the blood was cultured within 48 hours of the completion of the therapy at which time, also, the urine and faeces were cultured, and these cultures were repeated subsequently at weekly intervals, until the patient was discharged.

TOXIC EFFECTS OF TREATMENT

During the treatment, nausea and vomiting occurred in three cases. There were no other toxic manifestations of sulphathiazole. Even with the massive doses of penicillin administered, no toxic effects such as urticaria, itching or dermatosis were observed in any of the cases. The frequency of pain at the site of injection could not be assessed owing to the toxic state of most of the patients. In one case, a miscarriage occurred on the third day after the institution of the combined therapy. It is difficult to say whether this was due to the stimulating action of penicillin on the uterus (Kolmer[9] 1947) or due to the disease.

RESULT OF PENICILLIN-SULPHATHIAZOLE THERAPY (Table 2)

This treatment was given to 18 patients. In two of the cases, the course of therapy was repeated. Eight of these patients were in a severely toxic state before the commencement of the treatment. The toxicity was judged by the general condition of the patient, *i.e.*, consciousness, delirium, dehydration. Of this series of eighteen, four patients expired. Three of these were severely toxic before the commencement of the treatment and had a tendency to hyperpyrexia. The cause of death in these three cases was hyperpyrexia occurring on the second or third day of the beginning of the treatment. The hyperpyrexia may have been due to the disease (as these cases showed a tendency towards it from the beginning) or due to the treatment as foreseen by Bigger[3] (loc. cit.). The fourth case showed a temporary improvement after the treatment but died of intestinal perforation several days later.

Of the 14 cases that recovered, a marked improvement was shown after the treatment, in their general condition. In three cases the temperature came down to and remained normal at the end of the course. Subsequent cultures from blood, urine and faeces in these cases were negative. In one case (Case No. 2) the therapy of five days duration having produced very little effect on the course of fever, and the blood culture remaining positive, the treatment was repeated after an interval of seven days. At the end of this second course, the temperature fell rapidly to normal and the cultures from blood, urine and faeces were negative. In the other case (Case No. 14) in which the therapy had to be repeated, the first course of treatment had a beneficial effect on the temperature, and the blood culture became negative, but the urine culture, which had also been positive before treatment remained positive. This patient relapsed with a positive blood culture after seven days of normal temperature. The second course of therapy was given during this relapse which was almost as severe as the original attack. The therapy had beneficial clinical results and the temperature came down to normal three days after the completion of treatment, though the blood culture taken immediately after the end of the course, was positive. In the remaining nine cases there was no immediate fall in temperature, but the course of the disease appeared to have taken a change for the better, as indicated by a decrease in toxicity, a subjective mental outlook, an absence of complications, and a rapid convalescence. Complications like pneumonia, broncho-pneumonia, parotitis commonly due to penicillin-sensitive organisms were effectively prevented. The detailed results are presented in Table 2.

Convalescence—It was observed that the patients who recovered after this therapy showed a comparatively rapid convalescence, being able to take a full diet early, to feed themselves, to sit up in bed, and later to walk about in only 2 to 7 days after their temperature became normal. This may be ascribed to the absence of any of the usual secondary complications and to a lessening of the toxicity, the patient thereby being enabled to be given a more solid diet during the whole course of the fever, thus preserving his strength.

BASIC TREATMENT

Every patient regardless of the special therapy was given a line of treatment as decribed below:—

On admission the daily fluid intake and output were measured and charted. Every attempt was made to induce the patient to drink from 120 to 150 ozs. of fluid in 24 hours (out of which 40 ozs. consisted of milk, 16 ozs. of tea, 12 ozs. of fruit juice and the remaining of water).

In some toxic and dehydrated patients, subcutaneous 5% glucose saline was administered in a quantity of 500 c.c. to 1,000 c.c. In cases developing intestinal haemorrhage, blood transfusion was given but other than this, no injections (glucose, vitamin C, coramine) were given as a daily routine. The other complications were treated on more or less orthodox lines. The patients were encouraged to eat solid food such as soft bread and butter, soft rice, bananas, at any stage of the illness, regardless of the presence or absence of fever.

Due to the early feeding in the above manner the patients had strength sufficient to sit up in bed within a day or two of the temperature reverting to normal and within the course of another five or six days were able to walk about. All the "control" cases were given this basic treatment only. The detailed results are presented in Table 3.

DISCUSSION

PENICILLIN-SULPHATHIAZOLE TREATMENT. Parsons[12] (1948) reported the results of cases treated in the British Army personnel in the Middle East with combined Penicillin-Sulphathiazole therapy. The dosage advocated by McSweeney was not strictly adhered to. He bases his results on the reports of the doctors and nursing sisters who were in immediate charge of the patients. Very few rapid cures were obtained and the author was disappointed with the results. He ascribed the failures partly to non-adherence to McSweeney's dosage schedule.

The penicillin-sulphathiazole treatment was also tried by Bevan *et al*[2]. (1948) in a group of 39 cases in a recent outbreak at Aberystwyth (South Wales). It was claimed that the dosage of the drugs and the procedure in treatment recommended by McSweeney were closely adhered to *viz.*, two courses each comprising of 10 mega units of penicillin and 34 gms. of sulphathiazole were administered over a period of 4 days. They found that there was no disappearance of toxaemia and of organisms from blood, faeces, and urine, nor subsidence of pyrexia as described by McSweeney, compared to a group of "control" cases. The authors have been so disappointed with the results obtained that they warn against indiscriminate use of penicillin-sulphathiazole in the treatment of typhoid fever.

McSweeney[11] (1948) criticises both these reports on the method of treatment adopted. He also mentions 28 severe cases of typhoid fever successfully treated by himself, during the last 2 years, with 2 courses each, consisting of 12 mega units of penicillin and the usual dosage of sulphonamides with 2 days' interval in between. From his experiences he still maintains that combined penicillin-sulphathiazole therapy is a promising line of treatment in typhoid fever.

Of the 18 cases treated with combined penicillin-sulphathiazole therapy in this series, only one was given a double course as recommended by McSweeney but with a longer interval viz., 7 days. Of the 4 deaths that occurred, 3 cases were in a highly toxic state when the treatment was started and died before the treatment could be completed, the fourth was apparently recovering after the treatment but died later of perforation. There was a definite diminution of toxaemia, and subsidence of pyrexia in the remaining 14 cases. The present series is too small to allow of definite conclusions. It may yet be said that the therapy does diminish the toxaemia and produce a steady low trend in temperature which is all that is expected by McSweeney.

INTRAVENOUS BACTERIOPHAGE TREATMENT.—The bacteriophage used in the present series was an unslected 'stock' phage. The results obtained are therefore not comparable with those reported by Knouf *et al*[8]. (1946) after using type-specific Vi phage. But they are very similar to those obtained by Bower[4] (1948) during the earlier period when unslected stock phage was used for therapy. In some of their cases, the course was modified; in the others it was not. In some cases the results were so spectacular as to encourage further study.

Banerjee[1] (1939) also used stock bacteriophage which was administered intravenously. He repeated the therapy on two or three successive days, increasing the dose each time. At the end of three days' treatment, the temperature in each case became normal and remained so.

In the treatment of his 3 cases, Banerjee[1] (1939) did not use the drip method as used by Knouf *et al*[8]. (1946) and in the present series. Rigors which occurred in all these series after the injection of the bacteriophage were more or less similar.

As identical methods were not used in the preparation or administration of the phage, it would be difficult to compare the results obtained in the three series, though in each series, the therapeutic action of the phage has been found useful. It may be suggested, however, that in future trials, type-specific Vi bacteriophage should be used and administered by intravenous drip, and repeated on successive days if necessary.

CASE REPORTS

(1) Case No. 1 (table 2)—Male W. D., aged 21 years, was admitted for a continuous fever of 21 days' duration and delirium. He was toxic, drowsy, and on examination had bronchitic signs in the lungs. Liver and spleen were not palpable. His tongue was coated. The white blood cell count on admission was 400/c.mm. with neutrophiles 55%, eosinophiles 3%, monocytes 15%, and lymphocytes 27%. Widal reaction of the blood taken on the day of admission was positive in a dilution of 1 in 25 for 'H' agglutinins of S. *typhi.* The blood culture taken on the 22nd day of fever was found positive for S. *typhi.* Penicillin-Sulphathiazole treatment was instituted immediately. It was given for five days, making a total dosage of 12 million units of penicillin and 45.5 gms. of sulphathiazole. The temperature dropped down to normal within 24 hours of the completion of the treatment and after a reactionary rise lasting for about 48 hours settled down to normal as shown in the accompanying chart (Chart No. 1). There was a marked improvement in the general condition of the patient, who, only a few days previously being both drowsy and delirious, now started taking an interest in his surroundings and asking for food. His convalescence was rapid and uneventful.

(2) Case No. 2 (table 2)—Male C. G., aged 23 years, was admitted for fever with a history of chills, headache and bodyache of 2 days' duration. The tongue was coated. The spleen and the liver were not palpable. He developed rose spots in the second week. White blood cell count was 4100/c.mm. with a differential count of neutrophiles 68%, lymphocytes 30% and monocytes 2%. S. *typhi* was isolated in culture from blood collected on the 3rd day of fever. The Widal reaction on the same blood sample was positive for S. *typhi* in a dilution of 1 in 25 for 'O' agglutinins. He was given a combined course of penicillin-sulphathiazole lasting for 5 days. The blood culture taken after the therapy was positive for S. *typhi* and hence the course was repeated on the 19th day of fever. The temperature came down by lysis in four days as shown in temperature chart No. 2. The subsequent blood, urine and stool cultures were negative. The while blood cell count at the end of the first course was 6100/c.mm. with neutrophiles 72%, lymphocytes 24% and monocytes 4%. The convalescence was rapid and uneventful.

(3) Case No. 16 (table 2)—Female E.D., aged 12 years, was admitted for 7 days' continuous fever with chills, and headache, cough and diarrhœa. Liver was not palpable. Spleen was just palpable. Rose spots were present. Tongue was coated and there were bronchitic signs in the lungs. The total leucocyte count 3900/c.mm. with a differential count, neutrophiles 64%, lymphocytes 33%, and monocytes 3%. Widal reaction was positive for 'O' agglutinins in a dilution of 1 in 250. S. *typhi* was isolated in culture from blood collected on the day of admission. She was given penicillin-sulphathiazole treatment lasting for five days, with a total dosage of 12 million units of penicillin and 45.5 gms. of sulphathiazole The temperature came down to and remained normal at the end of the treatment.

The patient who was toxic and drowsy before the treatment rapidly improved in her general condition. Subsequent cultures of the blood, urine and faeces were negative. The white blood cell count at the end of the therapy was—total 7600 /c.mm., with neutrophiles 50%, lymphocytes 46% and monocytes 4%.

(4) Case No. 3 (table I)—Female M.M., aged 20 years, was admitted for continuous fever for 8 days, cough and vomiting. She was slightly toxic, the tongue was coated and the spleen was not palpable. Temperature 102° F, Pulse 90 per min., R. 26 per min. The total leucocyte count was 4000 /c.mm., the differential leucocytic count was neutrophiles 70%, lymphocytes 28% and monocytes 2%. The urine was normal and the intradermal test to the bacteriophage did not show reaction. S. *typhi* was isolated from blood culture collected on the 9th day o fever. On the 13th day of fever the bacteriophage was administered by intravenous drip method in a dose of 1 cc. diluted in 400 cc. of 5% glucose saline. At the time of starting the general condition of the patient was good and she had no complications. Blood pressure was 100/60 mms. Hg. T. 100.6°F, P. 112 per min., R. 28 per min. at the time of instituting the therapy. The patient had at the end of one hour a severe rigor lasting for about ten minutes and she almost became pulseless and her condition gave cause for anxiety. The temperature then started rising and the pulse volume became normal. In half an hour the temperature rose to its maximum *i.e.*, 104.4°F (in the axilla) and then started falling gradually. It touched normal after about 8 hours of starting the phage. Except for a short rise of temperature 48 hours later, the temperature remained normal, throughout, (temperature chart No. 4), and the patient had an uneventful recovery. The very next day after the phage she complained of intense hunger and was given light solid diet. The subsequent blood, urine and stool cultures were negative.

(5) Case No. 8 (table I)—N. M., male aged 18 years, was admitted for 9 days' of continuous fever. He had diarrhœa and anorexia. The tongue was normal and not coated. He had no rash and the spleen and liver were not palpable. Temperature 103.5°F, Pulse 128 per min., R. 40 per min. Total leucocytes was 12,500/c.mm. with a differential count of neutrophiles 58%, lymphocytes 38%, monocytes 2%, and eosinophiles 2% (probably the leucocytosis was due to accompanying nasal sinusitis). S. *typhi* was grown in culture from blood collected on 12th day of fever. Urinalysis showed presence of albumin, pus cells, and granular casts. Intradermal test to bacteriophage did not show any reaction. On the 20th day of fever, 2 c.c. of bacteriophage was given intravenously diluted in 400 cc. of 5% glucose saline: The patient had a rigor which continued for half an hour. The pulse volume became feeble but was palpable. The respirations were laboured but there was no cyanosis. The maximum temperature reached was 104.2°F, 3 hours from the beginning of treatment. Within 8 hours the temperature came down to normal and remained so for 48 hours. After a low fever of 4 days, the temperature settled down to normal. (Temperature Chart No. 5) The patient who had been very toxic and drowsy before the treatment showed immediate improvement in his general condition and recovered without any complication. The subsequent blood, urine and stool cultures were negative.

SUMMARY

(1) 18 culture positive typhoid fever cases treated with penicillin-sulphathiazole combined therapy, 14 similar cases treated with specific stock bacteriophage administered intravenously and 18 culture positive "control" cases which were not given any special treatment are reported.

(2) The penicillin-sulphathiazole therapy reduced the incidence

of secondary complications, lessened toxicity and in some cases shortened the course of fever.

(3) The intravenous bacteriophage therapy is promising.

(4) The results of both therapies are sufficiently encouraging as to warrant further trials.

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TABLE NO. I.

Cases treated with Bacteriophage

Case No. and initials.	Toxicity		Blood Culture		Bt. phage cc.	Day on which Treatment was started.	Results.
	Before.	After.	Before.	After.			
B. 1. P.K. ..	nil.	nil.	+	+	1 cc.	13th day.	C.
2. R.R. ..	+++	++	+	Neg.	1 cc.	14th day.	C.
3. M.M. ..	nil.	nil.	+	Neg.	0.5 cc.	13th day.	C.
4. A.G. ..	++	+	+	Neg.	1 cc.	24th day.	C.
5. L.P.D. ..	+ +++	+ +++	+	+	1 cc. 1 cc.	20th day. 25th day.	E.
6. P.B. ..	+	nil.	+	+	1.5 cc.	9th day.	C.
7. B.J. ..	+	+	+	+	1 cc.	14th day.	C.
8. N.M. ..	++	nil.	+	Neg.	2 cc.	20th day.	C.
9. R.F. ..	+	nil.	+	+	1 cc.	9th day.	C.
10. K.H. ..	nil.	nil.	+	+	1 cc.	13th day.	C.
11. S.R. ..	++	+	+	Neg.	1 cc.	15th day.	C.
12. D.S. ..	++	++	+	+	2 cc.	17th day.	C.
13. G.P.L. ..	+++	+++	+	+	2 cc.	15th day.	C.
14. M.J. ..	+	+	+	Neg.	1.5 cc.	20th day.	C.

TABLE NO. 2.

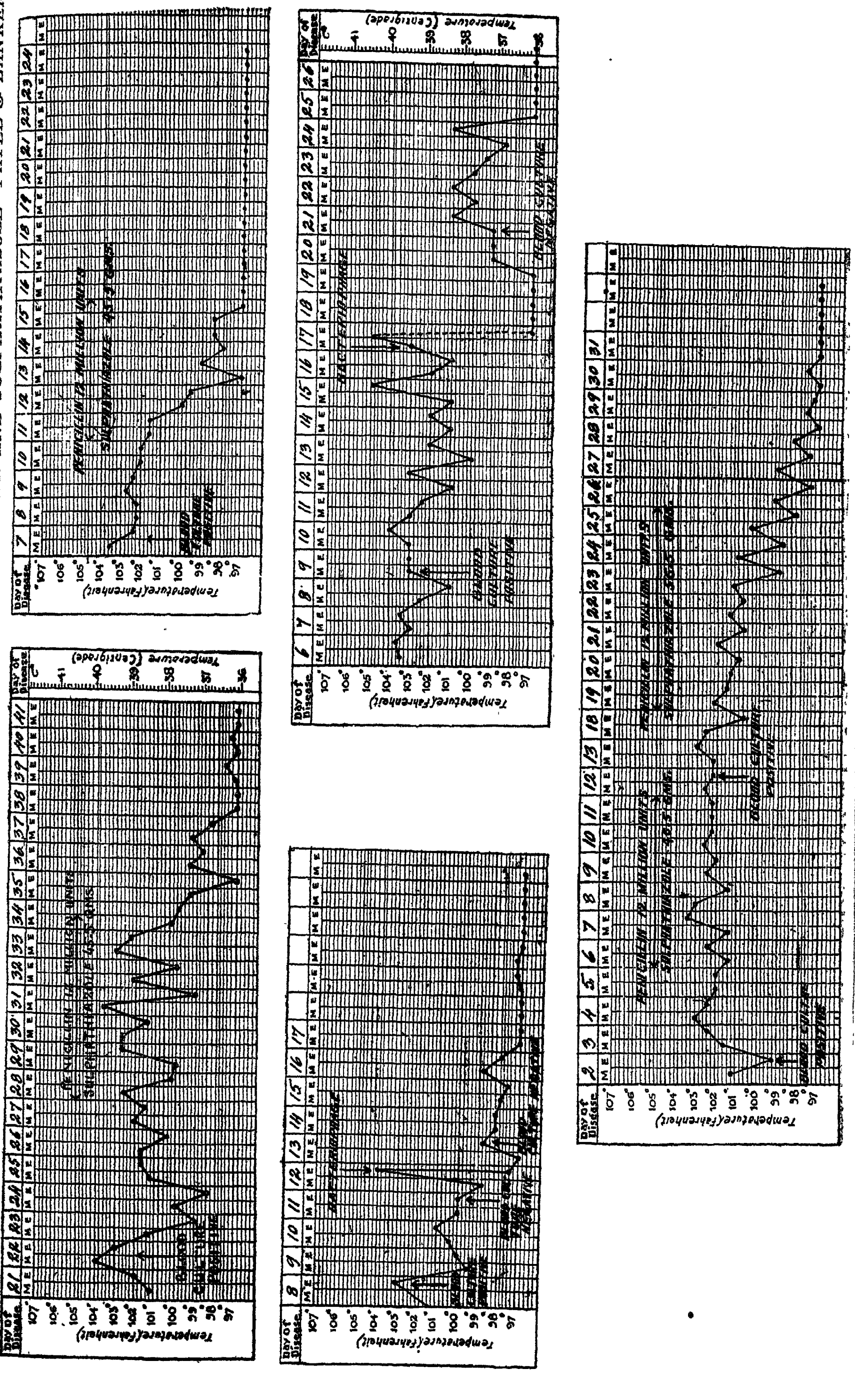
Cases treated with Penicillin-Sulphathiozole

Case No. and initials.	Toxicity		Blood culture		Treatment			Day on which Treatment started.	Results.
	Before.	After.	Before.	After.	P units million.	S gms.	Duration days.		
P. 1. W.D.	+	..	+	Neg.	12	47	* 5	28th day.	Cured.
2. C.A.G.	nil.	nil.	+ +	+ Neg.	12 12	47 47	5 5	6th day. 19th day.	Cured.
3. M.K.	+++	+	+	+	12	47	5	31st day.	Cured.
4. M.M.D. ..	+++	+++	+	..	2	11	1	12th day.	Died.
5. A.D.	+++	+++	+	..	7.5	29	3	11th day.	E.
6. M.F.	nil.	nil.	+	Neg.	12	47	5	24th day.	C.
7. F.E.D. ..	+	nil.	+	Neg.	11	29	7	13th day.	E.
8. M.R.	+	nil.	+	Neg.	12	47	5	17th day.	C.
9. R.K.	++	nil.	+	Neg.	12	47	5	18th day.	C.

Case No. and initials.	Toxicity		Blood culture		Treatment			Day on which Treatment was started.	Results.
	Before.	After.	Before.	After.	P units million.	S gms.	Duration days.		
10. K.R.	+++	+++	+	..	7	14	3	10th day.	E.
11. K.N.S... ..	nil.	nil.	+	Neg.	12	52	5	11th day.	C.
12. R.P.	nil.	nil.	+	+	10	51.5	4	11th day.	C.
13. S.H.	+	nil.	+	+	10	38	4	12th day.	C.
14. B.J.	+++ +++	nil. nil.	+ +	Neg. +	17 8	63 29	7 3	29th day. 57th day.	C.
15. D.V.	+++	nil.	+	+	12	47	5	25th day.	C.
16. E.D.	++	nil.	+	Neg.	12	47	5	11th day.	C.
17. S.S.	+	nil.	+	Neg.	14	61	6	12th day.	C.
18. W.L.	+	nil.	+	Neg.	11	42	4½	14th day.	C.

Case No. and initials.	Sex.	Toxicity.		Blood culture.	Urine culture.	Stool culture.	Results.
		On admission.	After 7 days.				
C. 1. B.D. ..		....	....	S. typhi.			C.
2. J.D. ..		nil.	nil.	S. typhi.			C.
3. L.F. ..		+	nil.	S. typhi.			C.
4. R.R. ..		+	nil.	S. typhi.			C.
5. D.B. ..		+	nil.	S. typhi.			C.
6. B.V.H. ..		++++	++++	S. typhi.			E.
7. G.C. ..		+	+++	S. typhi. Pneumococcus.			E.
8. P.D. ..		+	+++	S. typhi.			E.
9. V V. ..		+	+	S. typhi.			C.
10. A.M. ..		+	nil.	S. typhi.			C.
11. E.A. ..		+	+++	S. typhi.			C.

Case No. and initials..	Sex.	Toxicity		Blood culture.	Urine culture.	Stool culture.	Results.
		On admission.	After 7 days.				
C. 12. K.S. ..		nil.	++	S. typhi.			C.
13. G.B. ..	M	+	++	S. typhi.	Neg.	Neg.	C.
14. W.G. ..	M	+	+++	S. typhi.	S. typhi.	Neg.	C.
15. G.D. ..	F	++	nil.	S. typhi.	Neg.	Neg.	C.
16. B.M. ..	M	+	+	S. typhi.	Neg.	Neg.	C.
17. S.V. ..	F	+	+	S. typhi.	Neg.	Neg.	C.
18. M.R. ..	M	+	++++	S. typhi.	Neg.	Neg.	E.
19. R.T. ..	M	nil.	+	S. typhi.	Neg.	Neg.	C.
20. R.M. ..	F	nil.	nil.	S. typhi.	Neg.	Neg.	C.
21. S.T. ..	M	+	+++	S. typhi.	Neg.	Neg.	C.
22. M.R. ..	M	+	+++	S. typhi.	....	....	E.
23. B.M. ..	M	+	+	S. typhi.	Neg.	Neg.	C.
24. M.O. ..	F	+	++	S typhi.	S. typhi.	S. typhi.	C.



TEMPERATURE CHARTS OF PATIENTS TREATED WITH BACTRIOPHAGE PENICILLIN AND SULPHATHIAZOLE—PATEL & BANKER

MEDICAL PROGRESS

" ANTIHISTAMINE DRUGS "

K. U. Jhatakia *

Since the realisation of the fact that liberation of Histamine plays a part in many pathological conditions, the energy from all quarters was concentrated to find out the ways of counteracting its effects. Fourneau and Bovet[6] showed that certain phenolic alkylamine ethers had histamine inhibiting properties in guineapig's intestine preparations. This work created keen interest because of want of any specific therapy in many allergic conditions, where histamine is considered responsible for mischief. Treatment in such allergic conditions is less standardised than in any other group of medical conditions due to lack of knowledge about definite fundamental cause of these conditions. But recently more evidence has accumulated to show that some features of the allergic reaction are associated with liberation of histamine. This has stimulated the research to find the drugs that counteract the effects of histamine.

The discovery of really potent antihistamines is mainly due to Bovet and his colleagues in the Pasteur Institute in Paris. The first of the new antihistamines to attract the attention was 929F or Thymoxyethyl-diethylamine[5]. The more active drugs discovered later were mostly modifications of this original substance. Code[3] has recently contributed an excellent historical review of these compounds. Loew and his associates[9] and others have studied a number of compounds, some of which possessed a high antihistamine activity and relatively low toxicity in animals. All these antihistamines are drawing together and focussing clinical attention on their utility in various diseases in which abnormal histamine metabolism plays a role.

Since Dale and Laidlaw (1911)[19] clearly established the fundamental facts about histamine actions, much energy has been concentrated to study the various details about it. The important actions of histamine are: contraction of smooth muscles of bronchioles, vascular system, intestines, and uterus; dilatation and increased permeability of capillaries in the skin and mucous membranes; stimulation of secretion in lacrimal, nasal, pulmonary and digestive glands; and production of pain or pruritus through action on endings of pain nerves in the skin. When these actions combine they exhibit special syndromes such as hay-fever in nasal chambers, asthma in the lungs, urticaria or angioneurotic oedema in skin and mucous membrane. Gaddum[5] has surveyed the pharmacological actions of histamine in detail and the methods to estimate histamine. Histamine, normally present in the tissues of the organs, is derived originally from histidine by decarboxylation. Histidine may be converted into histamine by bacteria either in the food before it is eaten or possibly in the intestine[5]. Numerous estimates have been made of the quantity of histamine in animal tissues with varying results. It is in large quantities in lungs and skin but most tissues contain it in varying amounts at various times[5]. Estimations are done from blood as it is easy to get blood samples. In blood, most of the histamine is in cells, plasma usually containing very little. Interpretations of total blood histamine estimations are difficult as variations in quantity might be due to either disappearance or destruction of histamine containing cells. It seems also that the histamine in the tissues cannot all be free. Something prevents it acting under normal conditions[6]. Methods which estimate histamine do not estimate free active histamine but only the total amount which can be extracted from tissues. Thus estimation of free histamine is a difficult problem still. Due to these reasons estimations of blood-histamine have not been as useful in the study of histamine as at one time expected.

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Many different methods have been used to study the release of histamine from tissues. Kellamay (1947) has recently reviewed the factors which control the release of histamine[5]. A large number of substances liberate histamine, such as trypsin. Injury to tissues irritant poisons, curare and stilbamidine also do likewise.[5] This liberation of histamine in the body accounts for the symptoms of allergy. The allergic reaction consists of a chain of reactions. When an antigen to which an allergic patient is sensitive enters the system, specific antibodies called reagins are formed. Fixed antibodies are located in the shock organs of the patient, and upon renewed exposure to the sensitising antigen, an antigen antibody (reagins) reaction occurs in these shock organs, leading to the release of histamine or a histamine-like substance which dilates the capillary blood vessels and induces smooth muscle spasm. These reactions manifest themselves as special syndromes according to the system involved.

A rational therapeutic approach to this problem is based on use of some measure which can interrupt one or more links of this allergic chain. This is done by avoiding or eliminating the offending antigen but, this is not always possible, as often this antigen is obscure. A second approach is to hypo-sensitise or desensitise the patient by repeated subcutaneous injections of graded amounts of offending allergen. This is also not always practical or possible. The third approach is to attempt to desensitise the patient to histamine. Special attention has been directed in recent years towards counteracting histamine through subcutaneous, intravenous and oral use of small quantities of histamine alone or towards immunizing the body against it by injecting an antigen prepared with histamine and protein. This has been only slightly beneficial in the control of some allergic conditions, such as migraine but not in others. The next approach to break this allergic chain reaction has been to administer the enzyme which is alleged to neutralise histamine and thus prevent tissue reaction. A good deal of enthusiasm was shown for such an antihistamine enzyme called histaminase. This efficiently neutralised the action of histamine in *vitro* but failed to do the same under clinical trials. This led to a search for a better approach—an approach by which one could inhibit the production of histamine, or neutralise the histamine when produced or inhibit its action in the body. A systematic research for such antihistamine measures was undertaken.

It is well known that many of the pharmacological actions of adrenaline are opposed to those of histamine. These two substances act as physiological antagonists and the body uses them as such. Dale thought that the vasodilator effect of small doses of adrenaline might be due to release of histamine[5]. Experiments which appeared to show that adrenaline does release histamine from the lungs turned out to be inconclusive. (Dale and Richards 1927). But the work of Staub supports the theory on which the experiments were based. Staub found that when 0.2 mgm. of adrenaline was injected intravenously in man, in nine minutes the plasma histamine rose from 10 to 150 mg. per litre. Thus injection of histamine releases adrenaline and injection of adrenaline releases histamine[5].

Other group of substances which are opposed to histamine are those which destroy it. Formaldehyde (Kendale 1927) destroys histamine in *vitro* and may oppose its action on an isolated organ CO_2, (Garon 1938) and nitrites (Gaddum and Schild) have similar action. There is no evidence that they do the same in vivo[5]. The other substances found to have some antihistamine action include peptamines containing histamine (Rocha e Silva 43), Iminazole, (Morris & Dragsted) picrotoxin, and nicotinamide.

Histamine itself works as its own antagonist. In the search for other antihistamines Edlbacher, Jucker, and Baur (1937)[5] tested many aminoacids and found that histidine, arginine and cysteine had some effect on high concentration.

The discovery of the really potent antihistamines is mainly due to Bovet and Forneum, who showed that certain phenolic alkylamine ethers had histamine inhibiting properties.

PHARMACOLOGY

Benadryl, the first antihistaminic agent to be widely used in clinical practice was introduced in 1946[9]. In France antergan has been used clinically since 1942[20]. At present many antihistamine drugs have been synthesised. They all have some chemical relationship to one another, which is evident from their formulae. Some of them are :—

(*a*) Benadryl; B. dimethylamine-ethyal benzhydryl ether hydrochloride
(*b*) Pyribenzemine monohydrochloride.
(*c*) Anthisan ; Pyranisamine maleate.
(*d*) Neo-antergan ; N—dimethyl—aminoethyl—N-benzylaniline.
(*e*) Antistin ; 2 (N-Phenyl-N-benzylaminomethyl)—imidazoline.

Recently Halpern of Paris[7], has reported on a new series of compounds, the thiodiphenyl-amine derivatives, which are more effective and less toxic in animal experiments than other drugs reported previously. Two compounds, 3015 RP (Dimethyl-aminoethyl-thiodiphenyl amine) and 3277 RP (dimethyl-amine-2-propyl-1-thiodiphenylamine) are found to be particularly potent.

Chemical formulae of some of these preparations are as follows :—

(1) Benadryl

$CHO\text{-}CH_2.N.(CH_3)_2\text{—}HCL$

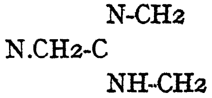
(2) Pyribenzamine

$CH_2\ N.CH_2CH^2.N : (CH_3)_2$

(3) Neoantergan

$CH_3\ N.CH_2.CH_2.N: (CH_3)_2$

(4) Antistin



$$N.CH_2\text{-}C\begin{matrix}N\text{-}CH_2\\ \\NH\text{-}CH_2\end{matrix}$$

(5) 929F

$CH_2\text{-}N(C_2H_5)_2$

(6) R. P. 3277

$CH_3\text{-}\ \ CH\text{-}N\text{-}S\text{-}CH_2\text{-}N(CH_3)_2$

A good deal of experimental work has been carried out to prove the antihistamine action of these compounds. Guinea-pig reacts to intravenous doses of histamine with characteristic bronchospasm and asphyxia difficult to distinguish from that observed in anaphylactic shock. The effect is rapid in onset and death from fatal doses occurs within a few moments. Post mortem examination reveals the characteristic pale emphysematous lungs in each instance. The protective effect of antihistamine drugs against lethal effects of histamine is striking and indicates a great degree of specific antagonism. Various investigations have reported that these compounds also exert marked antianaphylactic activity[4,19,20]. A comparison was made between four antihistamine substances, benadryl, pyribenzamine, antergan and neoantergan in affording protection to guinea-pig against fatal effects of intravenous histamine. All compounds afforded same protection.

5 to 6 times L. D. of histamine was necessary to kill all animals protected with 3 milligrams of benadryl or antergan per kgm. The same dose of pyribenzamine was able to protect some animals against as much as 35 lethal doses of histamine, while neoantergan protected some animals against as much as three times this amount of histamine[4].

Similarly acute and chronic toxicity was studied in various species of animals by administering the drug in various ways. Death was usually preceded by marked excitability and convulsious with pyribenzamine. In some animals a secondary depression varying from minutes to an hour or more intervened between the period of excitation and death.[10] White rats of both sexes were given a daily injection of pyribenzamine, 5 milligrams per kgm. and after five months there were no significant changes in red blood cells, white bloods cells, body weight and reproductive capacity[10]. Local toxicity was also studied and it was observed that intra-muscular injections of pyribenzamine, 0.1 c.c. of 5% Solution in gastrocnemii muscle of rats, resulted in replacement of muscle cells by fibroblasts[10]. This suggests that local necrosis may follow injudicious use of high concentrations of this drug hypodermically.

McGavack, Elias and Boyds[13] published results of extensive clinical study of 60 normal subjects and 242 patients receiving this drug. Positive effects were as follows :—

(*a*) Suppression of dermal response to histamine in all of 27 persons studied.

(*b*) Depression of gastric acidity in 20 of 21 subjects.

(c) An atropine-like action on the eye in 43 of 60 subjects on topical application of the drug in 0.5% solution.

(*d*) Decrease in blood pressure of more than 10 mm. Hg. in 29 of 74 patients when large doses were used, and orthostatic hypotension in 5 of these.

(*e*) Increased glucose tolerance after intravenous administration of a single 20 mgm. dose of benadryl.

Thus, pharmacological actions of these antihistamine drugs were studied in animals and later on in human beings. Three main actions were observed :

(1) They alleviate bronchial constriction caused by histamine and anaphylactic shock[9]

(2) They antagonise the spasm of smooth muscles[9]

(3) They prevent or overcome the vasodepressor effects of histamine[9, 19].

Voluminous literature has been published on pharmacological actions and therapeutic trials of various antihistamine drugs. The actions are practically the same, and reference to one applies equally to the other. A comparison of the pharmacological actions of these antihistamine drugs is made with other drugs acting on the same lines. Thus in relieving histamine-induced bronchial obstruction, benadryl is 15 to 30 times as effective as aminophylline. In reducing smooth muscle spasm it is 650 times more effective than papaverine hydrochloride. Loew[9] found benadryl as an antispasmodic a superior drug to atropine, papaverine and aminophylline. In addition to diminishing the depressor action of histamine and acetylcholine and augmenting the pressor action of adrenalin, Sherod, Schloemer and Loew[20] also found that benadryl decreases duodenal activity and has no stimulating effect on uterine activity. These drugs have some ability to block gastric response to histamine, as noted in dogs by Loew [9].

Following administration of benadryl, no abnormal change was observed in basal metabolism, circulation time, renal function, total red and white blood cell counts, haemoglobin, differential white blood cell counts, haematocrit readings, blood urea nitrogen, creatinine, glucose proteins, cholesterol, alkaline phosphatase, icterus index, van den Berg reaction or in cephalin flocculation test[12].

Many views have been put forward to explain the action of these drugs. The probable action is that they act by competition, *i.e.*, blocking the sites of action of histamine. The results of quantitative studies of the antagonism are compatible with this view. Bovet believes that not only the antihistamines but anti-adrenalines such as phenoxyethyl-diethylamine act in this way. Loew[16] objected that molecules of antihistamines and of histamine are so different that they would not be expected to combine with the same groups in tissues, but Gaddum[5] attempts to answer this objection.

These antihistamine drugs antagonize all actions of histamine, with the notable exception of its action on the gastric juice, which is very little affected. Most of the antihistamines are also good antagonists for acetylcholine, many of them have local anaesthetic effect, and mixed effects on the central nervous system which is excited in animals but depressed in man.

THERAPEUTICS

Clinical evaluation of any drug in allergic disease is made with great difficulty. Allergic manifestation are frequently self-limited, especially acute reactions. Even in such chronic conditions as perennial rhinitis and chronic asthma, spontaneous improvement may occur. This happens due to sudden disappearance of certain inhaled ingested antigens from patient's environment and because of the likelihood of spontaneous desensitization to certain antigens.Psychogenic influences also play some part.

Clinically the effect of these antihistamine drugs reflects their powerful antagonism to histamine, which has been observed experimentally. They do not chemically neutralise histamine nor do they prevent its production in the body. They are believed to compete with histamine in its affinity for the cells. Two actions stand out, ability to inhibit whealing and to dry up mucous secretion[9].

Clinical use of antihistamine drugs for induction and maintenance of symptomatic relief of various allergic and spasmodic disorders, is attended by favourable results in high proportion of cases. Various entities in which these drugs may be used for effective symptomatic relief, include urticaria and various other skin conditions, like dermatographia, erythema multiforme, contact dermatitis, hay fever, vasomotor rhinitis, serum reactions, drug sensitization, dysmenorrhœa. While the clinical effectiveness of these drugs has not been fully established in asthma, angioneurotic edema, eczema, migraine, pruritic dermatoses and radiation sickness, yet it is found useful in these conditions. Many papers have been published on results of trials with various drugs of this group.

The therapeutic dosage of these drugs is 50 to 100 milligrams by mouth, 2 to 5 times a day. This represents about 2 milligrams per kgm. of body weight per single dose. Single oral dose lethal to 50% of rats is 520 milligrams per kgm. of body weight, and so, a wide range of safety is present[19]. These drugs are given orally, by intramuscular injection and even by intravenous injection. Intramuscular administration of benadryl in solution containing 10 milligrams per c.c. can be used but it gives local pain and so it is used only in selected cases[19]. Oral dosage should not exceed 400 milligrams per day. Therapeutic effects in various conditions are as follows:—

(1) *Urticaria and Angioneurotic Edema*:—Various authors have published satisfactory results in urticaria in over 80% of cases[11], [14], [19], [20], [21], irrespective of whatever causes this urticaria. Patients with recurrent urticaria are also benefitted[15]. Schindler (1946) used the drug in various doses and found that 300 milligrams daily for 10 days were without any unpleasant effects. Brock (1946) treated chronic urticaria with relief after 2 to 3½ weeks' medication. Good results in cases of angioneurotic edema are also reported. McGovack and others[13] reported more than 90% of all patients with angioneurotic edema, generalised pruritus, urticaria and allergic hydrarthrosis as relieved with benadryl.

(2) *Pruritus*:—Schindler (1946) tried antistin in cases of pruritus due to different conditions, such as infective hepatitis, carcinoma of the duodenum, plasmocytoma, carcinoma of pancreas, lymphogranulomata and drug and senile pruritus. Most of them were relieved. Itching in cases of prurigo vulgaris, lichen ruber planus, psoriasis and after scabies also responded favourably[15]. Overton (1948) reported no relief in 14 cases of pruritus vulvae or one or both of idieopathic etiology[15].

(3) *Drug Rash* :—Good effects of these drugs are also reported in urticarial rash due to penicillin, sulpha group, insulin, liver extract, aspirin etc[9-20]. Taken prophylactically before skin tests, benadryl prevents dermographic whealing which is often encountered as an obstacle to skin testing in allergic practice[3].

(4) *Other skin conditions* :—James Overton (1948) observed good effects of antistin on the symptoms in various skin conditions such as acute and chronic urticaria, angioneurotic edema, chronic constitutional eczema, varicose eczema, contact dermatitis, lichen obtusus corneus, mycosis fungoides, while the drug was found ineffective in actinic dermatitis, cheiropompholyx, infantile eczema, erythema multiforme, dermatitis herpetiformis, lichen planus, pemphigus vulgaris, senile pruritus, pruritus valvae et ani, psoriasis, and urticaria papulosae. Summing up, he states that this type of drugs have only a limited usefulness in dermatology. They effect a symptomatic alleviation but not a cure.

(5) *Vasomotor Rhinitis* :—Relief in 20 to 80% of cases have been reported in this condition by various authors.[1, 19, 20, 21].

(6) *Common Cold*:—Brewster (1947) used benadryl for treatment in 100 cases of cold. It was found to relieve completely about 10% of such cases and to shorten the course and afford marked subjective relief to 95% of all cases. This was due to inhibiting effect upon serious discharge from the mucous membrane of upper respiratory tract and its soporific effect.

(7) *Hay Fever*:—75% cases of this condition are benefited with the drug[1, 6, 9, 21] Southwell [18] tried anthisan in proved hay fever cases after performing scratch test and found it successful in reducing the severity of symptoms in 15 cases. Blumenthal and Rosenberg reported good relief in all their cases with these drugs[9].

(8) *Serum sickness* :—Peterson and Bishop[16] have recently reported successful results in cases of serum sickness. 50 to 100 mgm. three times a day was sufficient.

(9) *Asthma* :—Results have been rather disappointing. Feinberg and Friedlander reported no improvement in 17 cases of asthma[3]. Partial relief was reported by Todd in a good number of cases but only few obtained complete relief.[19] Levin[8] reported symptomatic relief in 65 percent of asthma cases. Southwell[18] tried anthisan in 25 specially selected and carefully observed asthmatic patients without any apparent benefit. The drug is effective in incipient asthma, both in the infantile type characterised by edema in the lungs as well as in the pertusis-like cough of allergic bronchitis, which so often inaugurates asthma[20]. Severe attacks of asthma have been temporarily controlled by intravenous administration of these drugs when aminophylline and ephedrine have failed[20]. In my own series of 24 cases of bronchial asthma, the drug by intravenous

route did not bring any better results when aminophylline given intravenously had failed.

(10) *Allergic Shock* :—In allergic shock due to the accidental intravenous injections of antigens or in shock from ingestion or inhalation of antigens to which the patients are extremely sensitive, the action of the drugs is most impressive[20].

(11) *Dysmenorrhœa* :—Blumenthal and Rosenberg[9] reported relief in 7 out of 10 cases of functional dysmenorrhoea. According to Sellac[9] histamine even in extremely high dilutions is a powerful stimulant of the uterine musculature. If it can be proved that histamine content increases during menstruation, use of antihistmine drugs against dysmenorrhoea will rest on a sound physiological basis. The antispasmodic effect of these drugs in dysmenorrhoea is also reported[6,11].

(12) *Miscellaneous Conditions* :—These drugs produce good results in cases of acute histamine cephalgia [11], [19]. Experimentally prophylactic injections of benadryl prevent headache induced by histamine [20], yet in true allergic migraine and headaches associated with allergic sinus diseases, their effect is doubtful[20]. Todd[19] reports improvement in some cases of migraine, pulsating tinnitus and tension headache. In Meniere's syndrome 75 to 80% relief of symptoms were observed with these drugs[11]. Waldbott[20] noticed improvement in few cases of gastrointestinal allergy. In allergic conjunctivitis topical application of a 0.5% solution of the drug controls photophobia, itching, and lacrimation[20]. Fair response was noted in a case of trigeminal neuralgia[11]. Attempts to relieve gastric ulcer through the inhibition of gastric secretion by the drugs have failed as far[20]. Successful results have been reported in irradiation sickness[20]. The drugs were tried to prevent transfusion reactions as a prophylactic measure and they prevented severe reactions[9]. Good response is observed in spastic colon[9].

Recently Chatterji and Majumdar (J. I. M. A. 1949 : 99 to 101) reported a case of acute nephritis which improved dramatically with antistin orally when the usual line of treatment had failed. It seems that with penicillin and antistin type of drugs, we might be able to do much good in such kidney conditions which are otherwise so often intractable to treatment.

From all these findings, it is evident that the antihistamine drugs deserve an important place in treatment of allergic diseases. They are equal and in some cases superior to other older drugs, like epinephrine, aminophylline and epehdrine in the treatment of these conditions.

Side Effects and Their Management :—20 to 50 per cent of all patients taking antihistaminic drugs experience side effects such as drowsiness and dizziness, blurring of vision associated with a peculiar feeling of floating and being suspended[1,20]. Headaches, anorexia, nausea vomiting, giddiness, faintness, disorientation, diarrhoea, depression, fever, dryness in throat, muscular twitching, collapse and convulsions are other side effects[1], [6], [9], [20]. These manifestations are noted more frequently with benadryl and antistin than with pyribenzamine and neoantergan [20]. They may appear with the first dose and absent later or vice versa[20]. The reaction comes on with any dosage, but more commonly with larger doses[1]. These manifestions range from mild to serious disturbances, but are of a temporary nature.

Prolonged administration of the drugs for weeks and months has thus far not resulted in any demonstrable organic damage either in human beings or in animals[20]. So far there is no indication of cumulative action or of addiction to the drugs[20]. However, several patients have been encountered in whom there developed allergic manifestations from the antihistaminic drugs, namely dry allergic cough, urticaria, or dermatitis[20]. Aggravation of existing asthmatic wheezing is occasionally noted[20]. Nervousness, incordination and epileptiform convulsions are reported in a child of 3½ years age[15].

Side effects have been reported in varying proportions by different authors. Stroh (1946) found that 14.2% suffered from these side effects. McElin and Horton's (1945) reported that 60% complained of sleepiness, 16% of dizziness and 14% of nervousness. Leary and Forber noted that 33% of their patients suffered from toxic reactions[15].

Drowsiness is a common side effect and occurs often with benadryl. Among 696 patients treated with benadryl, 366 had drowsiness. This is minimised by administration of benzedrine sulphate 2.5 to 5 milligrams or by caffeine[9]. Dizziness, dry mouth, nervous feeling are not of great importance. These are seldom present to a degree warranting discontinuation of the medication. They often become less noticeable or disappear completely as therapy is continued.

Nausea is experienced in about 5% cases in which event a glass of milk or other beverage may be taken immediately before taking a second dose or the drug may be taken after meals[19].

Side effects from the intravenous use of the drug were similar to those after its oral use[9]. Almost all patients were drowsy and/or dizzy following the injection[9].

The severity of the side reactions in some cases indicate the imperative need for beginning with a small dose and increasing it slowly. This fact must be emphasised since deaths have been reported following the use of antihistamine drugs[1]. It is also reported that one drug of this group may produce side effects in a particular individual while the other drug of the same group may not show any side effect in this individual though it might produce same side effects in other patients[1]. It is also reported that one drug may fail in a case in which the other drug of this group might succeed[1].

A few considerations have to be borne in mind while using these drugs. Heart disease, hypertension, or renal disease when accompanied by the conditions mentioned above do not constitute contraindications to this therapy. While clinical experience with these drugs during pregnancy has been limited, its antispasmodic action on the nonpregnant uterus would allay suspicion of any untoward effect when administered during gestation[19].

Hypnotics or sedatives such as barbiturates or opium derivatives should be administered with extreme caution to patients being treated with these drugs.

A warning may be given against extravagant claims by over enthusiastic clinicians and patients, who are sometimes inclined to exaggerate the benefit obtained. It is unsound to administer any drug to allergic patients on a routine basis rather than when the particular need arises. Patients should be warned against driving a car or operating a moving machine, while taking these drugs, because accidents due to their side effects have already been reported[17]. It should be borne in mind that there is a possibility of development of sensitization to these drugs[20]. The greatest significance in their development is the new principle which has instigated their trial and which will lead to further knowledge of the mechanisms of allergic diseases and their therapeutic success.

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TUBERCULIN TESTING

Charlotte Simmons*

Epidemiological surveys attempt to locate tubercular infection in a population. Different methods are used to detect infected persons. A clinical examination aided by a radiogram enables one to discover many a case. Still many escape detection as the focus of infection in them may be neither extensive nor advanced enough to present clinical symptoms or produce changes in the radiogram. To detect these persons with minimal or early infection the tuberculin test is employed. The importance of this test has increased since the wider use of BCG vaccination.

Tuberculin, a glycerine extract of pure culture of tubercle bacilli, was introduced by Koch as a cure for tuberculosis. The name 'tuberculin' was suggested by Bujwid. Repeated observations and trials showed the failure of tuberculin as a therapeutic agent.

The use of tuberculin as a diagnostic agent is due to von Pirquet. His teachers Escherick and Epstein had observed local reactions at the site of infection yet they failed to understand the significance of these reactions. In 1907, von Pirquet reported, that if the skin was scarified under a drop of old tuberculin, a definite local reaction was obtained at the end of forty-eight hours in all those who were infected by the tubercle bacilli, while, in those who were not so infected, no such reaction was noticed. He considered this reaction to be an allergic phenomenon produced by the sensitisation of the tissues to the protein in the tubercle bacilli. To produce such a sensitivity only a few living bacilli were needed and they could be located in any part of the body. This test therefore, was a great advance as it enabled one to discover every infected person, however minimal the infection and however obscure the location. During the first decade following the description by Pirquet extensive testing demonstrated the high incidence of tuberculous infection among clinically healthy people and also showed that the number of positive reactors at different ages corresponded closely with the number showing tubercular lesions at autopsy when they died of causes other than tuberculosis. Similar was the experience of the veterinarians. All this confirmed the value of the test and today it is a specific test and is "considered to have no superior in the diagnosis of any disease" (Myers).

Various workers set out to improve on the Pirquet test—on its technique and on the material used for the test. Scarification was not always acceptable and the drop did not lend itself to the standardisation of the dosage. Mlle. Mantoux described the intracutaneous method, now called the Mantoux Test. She injected 0.1 c.c. of a varied dilution of old tuberculin intradermally and read the reaction forty-eight hours later. The dilution varied from 1 in a 1,000 to 1 in 10. Comparing the original with the Mantoux test it was found that the latter gave as reliable results as the former which it gradually replaced in practice. To simplify the test still further, Moro, in 1908, rubbed into the skin an ointment containing equal parts of old tuberculin and hydrous wool fat. This method did not become popular. As an improvement on this, Vollmer[24], in 1930, described the Patch Test in which a piece of filter paper soaked with tuberculin was applied to the previously cleaned skin. In 1931, Malmberg and Fromin[15] of Scandinavia, mixed tuberculin with adhesive plaster and applied it to the skin. Grozin[9], in 1933, modified it as a "visible tuberculin test". A similar modification has been suggested by Grubb[3] who recommends placing the tuberculin on a small film of photographic material from which all emulsion and antihalation has been removed.

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Research was also directed on tuberculin, to obtain a product which would be more stable, more uniform in its potency and which would produce the minimum side reactions. Since it was recognised early that it was the protein of the tubercle bacilli that was responsible for the reaction, search was directed towards this protein fraction. Seibert[19, 20] prepared a purified protein derivative, PPD, which had none of the drawbacks of old tuberculin, but all its qualities plus stability and greater potency. A concentrated filtrate from cultures of tubercle bacilli grown on synthetic medium was freed of the excess of salt and glycerol present by means of ultrafiltration, and was precipitated by trichloracetic acid. The acid was removed with ether, and the product simultaneously washed with ether. This was called the Purified Protein Derivative of tuberculin. This method was further modified to obtain a product far more pure chemically and twice as potent biologically. PPD has now replaced old tuberculin greatly, if not completely, in the Mantoux Test, though Vollmer and Goldberger found the latter more satisfactory for the patch test.

TESTS IN USE

Today the tests universally used are the Mantoux Test and the Patch Test.

MANTOUX TEST. After cleaning the skin of the forearm with ether or acetone 0.1 c.c. of the diluted old tuberculin or solution of PPD is injected intradermally with a tuberculin syringe. If the injection is correctly made a wheal, pale, with orange-peel appearance, about 2 mm. in diameter, is raised at the site of the injection. The injection is painful. The reaction is read after forty-eight and seventy-two hours.

PATCH TEST. After cleaning the skin of the back in the interscapular area with ether or acetone, the patch is applied to the skin. Any part of the body may be chosen, but for children the above site is better as it is not easily approachable. The patch is removed at the end of forty-eight hours and the reaction read then and after seventy-two hours.

MATERIAL

OLD TUBERCULIN. 0.1 c.c. of 1 in 10,000, 1 in 1,000, 1 in 100, 1 in 20, and 1 in 10 dilution containing 0.01 mg., 0.1 mg., 1 mg., 5 mg. and 10 mg. of old tuberculin are recommended, starting with 0.01 mg. and passing on to the next dose, if that one does not produce a reaction, till a reaction is obtained. The second test may be performed at the end of four days. In practice, except in very evident infection 1 mg. can be used as the first dose safely.

PURIFIED PROTEIN DERIVATIVE, PPD. This is two hundred times as potent as old tuberculin. It is available in two strengths 0.00002 mg. and 0.005 mg. For practical purposes 0.0001 mg. is a suitable first dose as it detects ninety-five percent of infected persons.

REACTIONS

MANTOUX TEST. For successful skin testing it is necessary to use a high grade tuberculin which has been recently tested for its potency and for the tuberculin to enter between the layers of the skin. The reaction is read after forty-eight and seventy-two hours making a note of the erythema and the oedema at the site of the injection. It is the degree of oedema that is more important. As there is a possibility of diversity in the interpretation, the National Tuberculosis Association of America has laid down the following for guidance :—

1. Doubtful (+ —) : slight erythema and a trace of oedema which measures less than 5 mm. in diameter.
2. One plus (+): erythema and oedema which measures 5 to 10 mm. in diameter.
3. Two plus (++): erythema and oedema which measures 10 to 20 mm. in diameter.
4. Three plus (+++): marked oedema and erythema which measures more than 20 mm. in diameter.
5. Four plus (++++): erythema and oedema as in above, plus central necrosis.

PATCH TEST. Vollmer and Goldberger[26] describe a positive reaction "as a sharply defined indurated, reddened square with lichenoid follicular elevations". They grade the reaction as :—

1. One plus (+) : a few lichenoid efflorescences.
2. Two plus (++) : lichenoid follicular eruptions assembled in a clear cut square.
3. Three plus (+++) : confluent eruption with marked induration and elevation in square form.
4. Four plus (++++) : spread of the cutaneous reaction beyond the square area and blister formation.

They recommend that though the reaction may be invisible on removing the patch it should preferably be read forty-eight hours later as then the specific re-action is more intensified and any irritation caused by the adhesive tape will have subsided.

DISCUSSION

No Reaction—Its significance. The response to a tuberculin test is an allergic phenomenon. Hence it takes some time for the sensitivity to develop ; the period may be as long as three months. A test performed during this pre-allergic period will be negative. Therefore the test has to be repeated again with all negative reactors. A negative reaction may be obtained in the presence of an old infection. In this case it may be due to waning of the sensitivity. With an active infection the test is negative in miliary tuberculosis, when a caseous focus erodes into a bronchus, when a subpleural focus empties itself into the pleural cavity and in far advanced and rapidly progressive tuberculosis. There may be a temporary decrease in sensitivity during the course of measles, influenza and during pregnancy.

Comparison of the Tests. As mentioned above when the Mantoux Test was introduced it was compared with the Pirquet Test. Having been proved to be as reliable, if not more, it was accepted as a good test. Naturally the same procedure has been applied to the Patch Test. Vollmer and Goldberger[24] (1937) reported the result on 209 tubercular children. In 187 out of these 209 there was conformity between the Pirquet Test and the Patch Test ; of the remaining 15 were positive to the Patch Test but negative to the Pirquet Test. Dean Stewart[22] reported 93.75 per cent conformity in 96 cases ; again, the remaining cases were positive to the Patch Test. Further observations on groups of 167 children and of 417 children by Vollmer and Goldberger [25,26] demonstrated that the Patch Test was as reliable as the Mantoux Test. Lowenthal[16] found that the Patch Test was equal in sensitivity to a 1 in 100,000 dilution of old tuberculin injected intracutaneously. Grant Taylor[23] reported comparable results on 94.3 per cent of 744 persons tested with the Mantoux and Patch tests. It is, therefore, evident that the Patch Test is both sensitive and reliable and it has the further advantage of ease of administration. The only drawback so far has been the cost, but with the BCG campaign in India it is now easier to secure the material.

Dose and Reaction. The percentage of positive reactors is proportional to the dose of tuberculin used. Jones[12] reported that the percentage of reactors to the first test of 0.000,1 mg. of tuberculin was 9.0 points higher than with 0.000,02 mg. and the area of reaction to the former was on an average 27 per cent broader, and 20 per cent longer and 53 per cent deeper than with the latter dose. Furculow[8]· *et al.* found the percentage of positive reactors rose from 12 percent to 100 per cent as they raised the dose from 0.000,000,01 mg. to 0.1 mg.

Cromin[4] *et al* found that with the simultaneous use of the first and second strength of PPD in a group of 1,003 children, 4.2 per cent reacted to the first strength and 18.2 percent to the second strength. It should be remembered that 0.000,02 mg. PPD is an adequate dose to detect all individuals with clinically significant disease.

Reaction and the Extent of the Disease. It is natural to explore the possibilities of utilising this diagnostic test as a quantitative test, to find whether the size of the reaction depends on the extent of the disease. With[29] found that the sensitivity was greatest in children with primary infection, the threshold being less than 0.01 mg. of old tuberculin, slightly lower in those with tuberculous pleurisy and still lower in those with healed primary tuberculous infection. It was the lowest in children suffering from miliary tuberculosis and tubercular meningitis. Clarke[2] did not find any relationship between the stage of the disease and the degree of sensitivity but noticed one between the duration and the sensitivity, the latter decreasing as the infection became older. Long[15] reports that "most surveys fail to disclose an obvious correspondence between the size of the reaction and extent of the disease ", but observes that "certain types of tuberculosis do lead to excessive sensitivity". Examples of these are tuberculous affections of the lymph nodes, and of the bones with excessive caseation. He also found that the reaction is ordinarily weaker in the case of well controlled recent infection without clinical disease, "the strongest reactions being given by young adults in apparent good health, but heavily exposed to infection." Furculow, Hewell and Nelson[8] testing the entire population of a sanatorium in Ohio found that all patients reacted to 0.1 mg. PPD, 466 out of 468 reacted to 0.000,1 mg. PPD, 84 per cent to 0.000,01 mg. PPD but only 12 per cent reacted to 0.000,000,01 mg. PPD. They also found that there were quantitative differences in the degree of sensitivity to tuberculin, this being in inverse relation to the severity of the tuberculous infection. Patients with pneumonic type of the disease were less sensitive than those with the fibroid type; those with fever, those who were clinically worse and those who died within six months of the test were also less sensitive. Howard, Johnston and Mitchell[11] studied 19 children with bone tuberculosis over a number of years and observed a rise of sensitivity to a high level with a subsequent fall, the higher level being maintained in those cases where the lesions fail to heal. In this study there were four children aged two years. Their first levels of reaction were 0.1 mg. in one and 0.01 mg. in the other three. They went up to a sensitivity of 0.000,001 mg. in two and the other two to a sensitivity of 000,000,01 mg. which levels they maintained over a period of three to seven years; as the lesions healed the sensitivity fell to 0.001 mg. or less. A high sensitivity was found by Dickey[6] in patients with phylectenules, lymph node and bone infections.

He also observed an increase in the size of the reaction in relation to the age of the child.

Duration of Tuberculin Sensitivity. When von Pirquet described the cutaneous test he was of opinion that the sensitivity to the protein of tubercle bacilli once created would be permanent. Subsequent observations have, however, thrown doubts on this. It has been found that the sensitivity declines with years in all those who are not exposed to further infection. Preliminary testing for BCG vaccination has demonstrated this. Calcified nodules have been found in persons negative to the tuberculin test. In them, it may be that the sensitivity has faded away with the healing of the first infection. Dahlstorm[5] studied the records of the Henry Phipps Institute to elucidate this question. Of 3,919 persons, 2 490 reacted positively. Of the latter, 276 or 11 per cent became tuberculin negative either transitorily or during the course of the study. There was a close relationship between the intensity of allergy and the disappearance of the reaction; only 0.4 per cent of 1,000 persons giving a three plus reaction with the first test became tuberculin negative while 70 per cent of 185 persons who gave a one plus reaction became negative. The study also revealed the influence of contacts on the duration of the sensitivity. In families with no tuberculosis 24 per cent became negative while of 63 reactors in families with cases of tuberculosis only one became negative. Contact may mean repeated mild infections and these may maintain the supply of living bacilli the existence of which seems necessary to sustain the sensitivity. Johnston *et al*[13] studied a group of children whose age varied from two months to nineteen years. They found that the sensitivity rose and declined following a parabolic curve, the period extending over approximately twenty months. "While in many instances the rise in this curve seemed to parallel absorption of the parenchymatous lesions and increasing involvement of the lymph nodes and its decline to follow the diminution in size and calcification of these nodes, nevertheless the fact that the same type of curve was found in cases which seemed to retrogress or remain stationary, made it seem likely that a change in allergy as observed in this simple uncomplicated type of first infection was independent of both the immune process and the anatomical pathology." In 828 reactors loss of sensitivity to 0.1 mg. was observed in 26 children and upto 1.0 mg. in twelve children. This occurred in a period varying from one to ten years with a mean of five during which there was no contact with the disease. In this series 17 of the 26 reactors lost their reactivity when calcification was evident for more than four years, six lost it coincidentally with the appearance of calcium and three without any evidence of calcification in the usual antero-posterior film. Mildred A. Norval[18] studied 112 children with a Ghon complex in the lung. 50.9 per cent reacted to the first dose of PPD and the rest did not, the non-reactors outnumbering the reactors in the age group of 13 to 15 years. This showed that there was a regression of sensitivity even in the presence of a Ghon complex unless there was a focus of living tubercle bacilli. In this series, of twenty patients with a history of exposure to tuberculosis, 75 percent reacted to the first strength of PPD. Similar decline in sensitivity has been noticed by Lloyd and MacPherson[14] and Aronson and Dannenberg[1].

Pseudo-Reactions. By increasing the dose of tuberculin, positive reactions may be obtained even in those who are definitely non-tubercular, and who have had no contact with tuberculosis. Of 553 non-tuberculous children aged 6 to 19 years 20 per cent reacted to the first dose of 0.000,02 mg. PPD but 96 percent reacted to 1.0 n g. Even among infants who were non-infected and who had no contact with tubercular persons 71.9 per cent reacted to 1.0 mg. PPD. Furculow *et al*[7]. are of opinion that reactions obtained with these large doses may be unspecific and not due to tubercular infection. Smith, Faulkner and Cordi[21] reported that 15 per cent of 207 children under 13 years of age who did not react to 1.0 mg. of old tuberculin responded to 10 mg. Vollmer and Ripps[28] retested 72 children who did not respond to 1.0 mg. of old tuberculin with 10 mg. of OT; in the second test 50 percent showed some sort of a reaction and 32 percent pronounced reaction after 24 hours. The reactions to 10 mg. observed by Smith[21] *et al* and Wollmer and Ripps[28] appeared and faded quickly; they reached their maximum size in about 24 hours and disappeared after forty-eight hours, a time when the specific reactions of tubercular infection are at their height. Vollmer and Ripps designate these reactions as pseudo-reactions. They are more frequent when purified protein derivative is used and hence the tuberculo-protein is responsible for them. In a person who has been infected with tubercle bacilli specific antibodies are formed which when they come in contact with tuberculin produce toxic reaction products called apotoxins. "A positive reaction to tuberculin is an allergic vascular reaction to apotoxin. At the site of the intracutaneous injection of tuberculin, apotoxin is not formed immediately but is gradually released over a period of time, which explains the prolonged course of the reaction illustrated as a plateau. On the other hand, high concentrations of tuberculin intra-cutaneously injected into persons non-allergic to tuberculin acts as an immediate primary irritant which the tissues rapidly dispose of " (Vollmer-Ripps).

Tuberculin Testing in relation to Radiograms. A comparison is made between the value of tuberculin testing and radiograms in case-finding. Crimm, Potts and Hudson[3] found the percentage of error essentially the same by the two methods. But discrepencies have been reported by other workers. Myers[17] found that of the 198 children who reacted to tuberculin 42.9 percent had definite roentgenological evidence of calcification, 21.7 percent questionable evidence and 35.4 percent no evidence at all. On the other hand, of 62 non-reactors 43.5 percent had definite evidence, 8.1 percent questionable evidence and 48.4 percent no evidence. Gass reported that in a group of tuberculin positive reactors 32.8 percent had definite radiological lesions while 24.7 percent of negative reactors had similar lesions. One of the limitations of the tuberculin test is the waning of the allergy after the initial infection gets older. But the radiogram has many more limitations. X-ray examination is usually confined to the chest but lesions may occur outside the chest; 12 percent of tubercular infections are extrapulmonary (Sweany). The shadows of the heart and diaphragm obscure a considerable part of the lung in the antero-posterior position and 31 percent of lesions are found located in these areas. For a shadow to appear on the screen it is necessary that the area of the disease must be macroscopic in size. Besides this, shadows seen on the radiograms are not diagnostic etiologically. Errors in interpretation occur often as the reading of the same picture, at the same time by different persons and, at different times by the same person, varies. Miller writes "with a technic of examination based upon careful study, calcification of tuberculous first infection in the thorax is demonstrable roentgenographically in only about one-fourth of the cases". X-ray examination has a total handicap of 80 percent in the detection of the lesions of primary tuberculous infection. Hence for case finding a tuberculin test is definitely better.

SUMMARY

The tuberculin test was first described by von Pirquet. He considered this an allergic manifestation. Von Pirquet's test was improved by Mantoux and further simplified by the Patch Test.

Old tuberculin has been supplanted by purified protein derivative PPD, for intracutaneous testing.

The Patch test is as reliable as the Mantoux test. The reaction depends on the dosage of tuberculin, or PPD, and the condition of the patient. The various factors that affect the reaction are mentioned.

The sensitivity to tuberculin is not permanent; it wanes with time unless there have been repeated fresh infections. The limitations of radiographic examination are described. Tuberculin test is today a specific test and is "considered to have no superior in the diagnosis of any disease."

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CASE REPORT

A CASE OF BIOVULAR TWINS : WITH ONE NORMAL CHILD, AND ANOTHER ANENCEPHALIC MONSTER ASSOCIATED WITH HYDRAMNIOS

Thakore V. Patel

The following case is reported because of its unusual features :—

Mrs. P. aged 22 years, para 2, was seen on 8th May, 1948, during the 30th week of her pregnancy for (1) unusual enlargement of the abdomen, (2) dyspnœa, (3) pain in the abdomen with general discomfort and sleeplessness. The respiratory, circulatory and nervous systems were found normal. There was obvious pallor of the face and integuments. On examination her blood pressure was 120/80 mm. Hg., and the urine did not show any albumin. The abdomen was greatly distended, and the fundus of the uterus had reached high upto the xiphisternum. The fœtal parts could not be made out, nor could fœtal heart sounds be heard. Kahn test of the blood proved negative. From the above findings a tentative diagnosis of hydramnios was made.

The patient was treated with diuretic drugs (potassium citrate and acetate), and the intake of fluids was restricted. She was also given orally, iron and liver for her anæmia, and sedatives (bromides and phenobaritone) for her discomfort and sleeplessness. However, there was increasing abdominal discomfort, and the dyspnœa became daily more pronounced. The skiagram of the abdomen revealed a hazy outline of a single normal fœtus lying in vertex presentation. On vaginal examination the cervix was found completely taken up, but the external os was closed; the presenting part could not be palpated, probably due to excess of liquor amnii.

It was decided to carry out abdominal paracentesis for the removal of the excess of liquor amnii, as suggested by Rivett[2], to relieve the patient's symptoms. This method was chosen because the skiagram had revealed a normal foetus, and we hoped that pregnancy might continue to full term after abdominal paracentesis.

This, therefore, was carried out on 10th June, 1948. It was found that the liquor amnii was not at all under increased tension which sometimes is the case, but the surprise was that hardly 14 ounces of liquor could be removed. The patient's discomfort and dyspnoea were not relieved, and therefore a medical induction of labour was now decided upon and carried out. Weak labour pains started the next day, and continued during the next 24 hours. The membranes ruptured at this stage, but not more than the usual amount of liquor amnii escaped. Five hours after the rupture of the membranes the patient delivered spontaneously of a normal living male-infant, weighing 5 pounds. After the delivery of the child, the uterus was found, to one's surprise, to have remained still of the size of full term pregnancy, but, on palpation, the fœtal parts could not be felt. Vaginal examination revealed a second bag of waters, which was very tense, and on rupturing it, about 8 pints of liquor amnii drained away. Now, on further vaginal examination, the parts of another fœtus could be felt, and it appeared that the face was presenting. Besides the presenting part, a soft cystic mass was felt, and in trying to make out its details, it ruptured and a small quantity of a clear fluid escaped: 25 minutes after the rupture of the second sac, the patient delivered spontaneously of a female anencephalic monster with a meningocele, weighing 4 pounds 8 ounces. The afterbirth delivered about 10 minutes after the birth of the second child. There were 2 placentae suggesting binovular twins. An injection of neogynergen 1 ml. was given after the expulsion of the placenta. There was no postpartum haemorrrhage, and the puerperium was uneventful.

COMMENT

(1) This was a case of binovular twins with hydramnios in which one child was normal, and had a normal sac, and the other child was an anencephalic monster, and acute-on-chronic hydramnios occured in the sac of this infant only.

(2) The skiagram of the abdomen did not reveal the presence of twins, and did not show the anencephalic fætus, due to excess of liquor amnii. (Abdominal paracentesis and removal of liquor amnii was therefore attempted in hope that the symptoms of the patient might be relieved and yet the pregnancy continued to term.)

(3) It is now obvious that we had tapped the sac of the normal infant and therefore only 14 ounces of liquor amnii could be removed with the consequence that the symptoms of the patient were not relieved. The hydramniotic sac of the anencephalic monster was probably lying behind the normal child and was not therefore tapped at all. We have not seen a difficulty of this kind in the treatment of hydramnios by abdominal paracentesis, recorded anywhere else.

(4) This case lends support to the theory of fœtal origin of liquor amnii in hydramnios.

(5) Incidentally it may be mentioned that the first of the twins is now 1 year and 3 months old, and is growing normally.

CURRENT MEDICAL LITERATURE.

MEDICINE

ONE HUNDRED CASES OF MILITARY AND MENINGEAL TUBERCULOSIS TREATED WITH STREPTOMYCIN. PAUL A. BUNN. The American Journal of the Medical Sciences—**216** : 286-315, 1948.

In this series majority of cases were given 1.8—2 gms. of Streptomycin intramuscularly per day divided into five to six doses. In cases of meningitis it was given intrathecally on alternate days.

The cases were divided into four groups. In group one there were 22 cases of miliary tuberculosis without any meningitis. Three cases died without any response, three cases showed a good response to start with but later relapsed and died. One case is alive but is in terminal stage. In five cases there was reduction in toxicity and reduction in the size of seedlings in lung fields. In nine cases there was complete resolution.

Second group consisted of ten cases of miliary tuberculosis which developed meningitis during or after streptomycin therapy. All these cases responded very well before developing meningitis. Once the meningitis developed its course was relentless. Nine cases died and in only one case there was resolution of lesions. Autopsy in these cases revealed healed or healing lung lesions and active brain and *pia* inflammation. In the 3rd group there were 25 cases of miliary tuberculosis with meningitis before any treatment was given. The results were as disappointing as in the previous series. 15 cases died without any improvement at all. In five cases there was marked clinical improvement for about two weeks but they relapsed and died. Four patients, though alive after two or three courses of streptomycin, are doing badly. In only one case there was resolution of lesions. Though the results were poor it was evident that prolongation of life for sometime was due to streptomycin.

The fourth group consisted of 43 cases of tubercular meningitis. Best results were obtained in this group. Sixteen cases died without any response to streptomycin at all. Eleven cases responded well but relapsed after six weeks and died. Autopsy of these cases revealed active lesions in meninges and brain with certain amount of organisation. Sixteen patients are alive and free from all stigmata of tubercular meningitis.

In this series toxic reactions were encountered in over 95% of cases. In 28% the reactions were serious and it hastened death in at least 5% of cases. Damage to the 8th nerve, to kidney, skin eruptions of various grades of severity and agranulocytosis were the most comman toxic reactions. An evidence of damage to 8th nerve was in 28% of cases. It is likely that at least in some cases the disease was the cause of this damage rather than the drug.

This study indicates that streptomycin is most useful in cases of tubercular meningitis. In all the acute types of tuberculosis it checks the disease for some time, increases the span of life of the patient for a few months to a few years but relapses are common and ultimate cure is not certain. With each successive relapse therapeutic response to the drug is poorer and poorer.

S. N. SHAH.

POLIOMYELITIS IN FAMILIES ATTACKED BY THE DISEASE. I. DISTRIBUTION OF VIRUS IN STOOL & OROPHARYNX OF MEMBERS IN HOUSEHOLDS. H. A. WENNER & WILLIAM, A. T. THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES **216** : 258-269, 1948.

A study of 24 members of five families was done to isolate the virus of poliomyelitis. There were 14 children and 10 adults. There was a paralytic case in each family. The material from throat swab and stool was innoculated intraspinally in the monkeys. The presence of virus was indicated by advent of paralysis and histological changes in the brain and spinal cord consistent with diagnosis of poliomyelitis in the monkey.

No attempt was made to find the source and how the infection occured, but the simultaneous appearance of illness in the families suggests a common source and simultaneous infection of all the members.

The virus was present in stools of 13 children and the 14th one whose stool was not examined had a paralytic attack. From 10 adults virus was found in only 4 of them.

Among these 24 persons there were seven frank cases of paralysis, seven had abortive attacks like transient weakness of a few muscles :—stiff neck, headache, vomiting, etc., and also tenderness of muscles. Seven persons suffered from indifinite illness like fever, headache, vomiting etc., and only three persons had no illness at all. This indicates how widespread is the virus. It shows that in a household with one paralytic case almost every child and 50% of adults are likely to harbour the virus at some time or the other, and children run a great risk of suffering from the disease.

The virus is easily detected from the throat of paralytic cases. It is present during or before the onset of illness and disappears quickly after the onset of paralysis. The stool remains positive for 3—18 weeks. Earlier the throat swab is taken greater are the chances of a positive result, irrespective of the severity of the disease.

What factors determine such a widespread dissemination is not studied but it is likely that spread is through a vehicle rather than through a person.

S. N. SHAH.

AN EVALUATION OF THE THYMOL TURBIDITY TEST: BY R. G. ERNST AND L. B. DOTTI. The American Journal of the Medical Sciences—**216** : 316-329, 1948. Fig. 3—Tables 9—References 13.

The Thymol turbidity test was performed by comparing the turbidity produced by adding 0.1 c.c. of serum to 6.0 c.c. of thymol barbital buffer, in a photoelectric calorimeter with standard barium sulphate suspension.

There was little change in the reading when normal and abnormal serum were stored at 10°C for fifteen days. Slightly higher values were obtained if the blood was taken after meal. The serum was inactivated by heating at 56°C for 30 minutes. The thymol turbidity value was lowered and cephalin cholesterol flocculation values were raised and both tests became inaccurate.

In 500 healthy controls 87% of readings were between 0-5 units with mean value of 3.2 and deviation of 1.8. This should be considered as fair degree of accuracy.

In 527 hospital patients suffering from diseases not involving liver 80% of cases had values between 0-5 units. There was a slight tendency to higher values. The mean value for this series was 3.7 with mean variation of 2.7. There was high incidence of higher values in patients with secondary syphilis, infectious mononucleosis, sickle cell anaemia with crisis, malaria, virus pneumonia and in-patients with cardiac decompensation. In cases of neoplasms, primary or secondaries in the liver, there was no elevation in the thymol turbidity value so long as there was no biliary obstruction.

All cases of infectious hepatitis gave positive results. The highest readings were obtained just before development of maximum jaundice. It falls very gradually and may take 6-9 months to return to normal. The fall or rise in the value of turbidity is a good guide to progress of the case. In one case of homologous serum jaundice the thymol turbidity value was high during icteric phase and quickly returned to normal with disappearance of jaundice.

In cases of cirrhosis of liver, so long as the liver parenchyma is functioning adequately thymol turbidity values remain normal. It has no relation to periportal fibrosis or the presence of ascites ; with hepatic failure turbidity value rises.

In all cases of chronic hepatitis one case of chronic amoebic hepatitis and two cases of subdiaphragmatic abscess with jaundice thymol turbidity test was positive.

In cases of chronic cholescystitis with cholelithiasis thymol turbidity test was positive in six cases out of eight with biliary obstruction but was positive in only one case out of eighteen with no biliary obstruction.

In order to compare thymol turbidity test with Hangers cephalin cholesterol flocculation test, both tests were performed in 308 normal controls 508 hospital patients, and 124 cases of hepatic and biliary diseases. In presence of jaundice both the tests are positive. Comparison indicated that cephalin cholesterol flocculation test is rather more accurate and thymol turbidity test is more sensitive. In majority of cases values given by both the tests are comparable.

S. N. SHAH.

MYOBROPHIC INDEX. KURULKAR, G. M., Ind. Jour. Med. Res . **26** : 295-334 Oct. 1948, 28 Refs.

17 Tables. 4 graphs and 2 appendices.

The author after reviewing previous work on anthropometric measure of an individual's nutritional status, which for one or other reason was not satisfactory has experimented with a new anthropometric formula which may possibly give better results. This new formula is a product of stature, full length and pelvic width in cm. and it is nearly double the body weight in grammes. The values of the C index which are representative of relative body bulk up to age of 22 years lie in a parabolic curve and march on in an unidirectional manner from thin type to plump type of individuals. The author has found some relation between thickness of skin and subcutaneous tissue at the anterior axillary fold and increase of C index. Muscular bulk can be found by deducting this thickness from C index. The C index with an age correction (from a table by the author) and with an adiposity correction can serve as a myotrophic index which in exercising bodies was found to be 0.86 and in non-exercising ones 0.79.

The myotrophic index suggested by the present author is based on a conception which combines Franzen's idea of nutritional status and Karl Pearson's three dimensional plea. The author hopes that further work along this line may lead to the solution of an efficient somatometric index of nutrition. The value of this myotrophic index can only be proved by its application by other workers.

J. C. PATEL.

SURGERY

PAINFUL AMPUTATION STUMPS AND PHANTOM LIMBS. TREATMENT BY REPEATED PERCUSSION TO THE STUMP NEUROMATA. W. RITCHIE RUSSEL, Oxford. B. M. J. June 11, 1949, 1024-1026.

The following considerations led to the trial of this method : 1. In the normal limb nerve endings in the skin are rendered insensitive by occupations which involve repeated minor trauma or prolonged firm pressure on the skin. 2. Conduction of a mixed nerve is easily interrupted by repeated pressure, without the production of any spontaneous pain. 3. The regenerating nerve fibres in an amputation stump are likely to be no less vulnerable to minor trauma or pressure than are normal nerves and nerve endings.

In the beginning the neuromata were first deadened with procaine and then percussed for 10 to 15 minutes with a wooden hammer. The present technique is to use a sphygmometer cuff to the amputation stump and inflate it to over 200 mm. Hg. Within 2 or 3 minutes the tender scars and neuromata become less sensitive, and gentle hammering with a wooden mallet can be done with increasing vigour for about 10 minutes. If the stump is too short for the cuff, hypalgesia of the neuromata can be obtained by prolonged pressure on them.

Treatment at first must be repeated at least twice a day, but soon one treatment a day is sufficient. A heavy mallet is required to treat neuromata buried under the thigh muscles.

A number of cases are described in which this method completely relieved the patients of their pain and disability.

E. J. BORGES.

TREATMENT OF HERPES ZOSTER WITH LIVER EXTRACT. H. S. GASKELL, B. M. J. June 11, 1949, 1037.

The author reports 20 cases which were completely relieved of pain due to Herpes Zoster with one or two injections of Liver Extract. In all cases the preparation used was "Neo-hepatex", administered intramuscularly.

E. J. BORGES.

ANAESTHELOGY

INTRAVENOUS DEMEROL—SCOPOLAMINE AMNESIA DURING LABOUR. BROWN J. M., VOLPITTO P. P., TORPIN R. Anesthesiology X 15-24, January 1949, fig. 4, Table 7, ref. 21.

Demerol (Pethidine) has been used in labour by many obstetricians since its preparation by Eisleb and Schaumann, but dosages and techniques have varied. In this report, Demerol 100 mg. and scopolamine hydrobromide 1/100 grain have been administered intravenously. This has been required to be given in majority of patients two or three times during the labour. The second intravenous injection of Demerol and scopolamine was required from two or four hours after the initial administration (average interval three hours) which was given when labour pain were of 40 seconds duration and were occurring at five minutes' interval. Primiparas required more number of injections. Few required four or five. No appreciable alteration of the course during the first stage was noted with the exception that patients frequently slept in between the pains and showed varying degrees too form activity with each pain. The second stage was characterised by hard prolonged uterine contraction with adequate relaxation and rest in between each pain. The second stage was rapid. Demerol as employed in this regime produced a sufficient degree of analgesia to reduce the restlessness of mothers markedly during labour, but not sufficient amount of analgesia consistently to abolish pain entirely. The incidence of apnea neonatorum was low.

J. C. PATEL:

THE UTILITY OF INTRAVENOUS PROCAINE IN ANESTHETIC MANAGEMENT OF CARDIAC DISTURBANCES. BURNSTEIN C. L.—Anesthesiology 10, 133-144, March 1949 15 refers.

Cardiac arrhythmias develop under general anesthetic agents. Tendency is towards downward displacement of pacemaker. Of 41 patients anesthetised with cyclopropane, some developed cardiac arrhythmia. In 33 most frequent abnormality consisted of extrasystoles. Clinically the anesthetist is in many cases unable to discern any irregularity in peripheral pulse whereas the electrocardiogram did show some irregularity. On the above grounds Burnstein injected procaine intravenously (1 per cent sol. and 100 mg. at a time). A maximum of 1000 mg. (1 gm.) was injected without any toxic effects. 10 cases are described in detail in which cardiac arrhythmias have developed. He summarises his paper as follows.

Case reports are presented to illustrate the utility of intravenous procaine in combating cardiac disturbances during general anesthesia. The dosage recommended is 100 mg. in a 1 per cent solution for an adult patient under general anesthesia. Corroborative reports from other clinics substantiate the above findings. Two patients whose cases are summarised here recovered from ventricular fibrillation following the intravenous injection of procaine. Intravenous procaine is also recommended as a prophylactic measure to minimise cardiac disturbances during general anesthesia. Cases are reported to show that with this technic cylopropane may be administered to patients with pre-existing cardiac disease without manifesting any apparent deleterious cardiovascular effects. Instantaneous recording electrocardiography is suggested as an added appliance to anesthesiologist's armamentariam. The importance of diagnosing cardiac arrhythmia properly is stressed.

J. C. PATEL

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Examples:

1. Coller, F. A., and Maddock, W. G.: The Function of Peripheral Vasoconstriction, Ann. Surg. **100**: 983-992, 1934.
2. White, J. C., and Smithwick, R. H.: The Autonomic Nervous System, pp. 271, New York, the Macmillian Company, 1941.

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THE SURGICAL TREATMENT OF BRONCHIECTASIS§

B. R. Billimoria*

The title of this paper is the "Surgical Treatment of Bronchiectasis". and I shall confine myself purely to the surgical aspects of the disease and not discuss points like the pathology, aetiology and diagnosis of bronchiectasis.

HISTORY.

The first successful lobectomy was performed in 1901, and Graham[3] in 1925, described his cautery technique of pulmonary resection. Graham[3] in his series of cases described an operative mortality of 11% with a further 22% late deaths. Lilienthal[4] in 1935 submitted 42 patients to operation with an operative mortality of 64%. Shenstone and Janes in 1932 evolved the tourniquet method of lobectomy. The late Mr. Tudor Edwards[2] of the Brompton Hospital, however, had recorded, three years earlier, a successful lobectomy using the dissection technique. It is largely the impetus given by his work that has led to the evolution of the present-day technique of dissection lobectomy. The tourniquet method of pulmonary resection has of course been abandoned owing to the many complications which follow sloughing of the distal stump of the lung. The dissection technique described by Tudor Edwards involves the individual isolation and ligature of the pulmonary artery and vein—the bronchus is then cleared and can be closed with precision. By this method the lobe is removed completely at its hilum and the secure closure of the bronchus avoids subsequent complications in the postoperative period. This method of lung resection has been extended to the segmental resection of an affected lobe. Robin Pilcher was amongst the first to point out the scope of segmental resection in cases of bilateral bronchiectasis. Sellors, Thomson and Qvist[7] published the first series of a hundred lobectomies (1944), and a large series of cases have now been published reporting an operative mortality of under 1%. It can be seen from this that vast advances have been made, within the last fifteen years in the field of thoracic surgery, and a thoracotomy is no longer regarded as a surgical feat. The operative mortality is no greater than the mortality involved in opening the abdomen for a major operation.

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§ Paper read before the Bombay Medical Congress, 1948.

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THE INDICATIONS FOR SURGERY IN BRONCHIECTASIS.

The indications for surgery in any disease have to be weighed against the prognosis if surgery is denied to the patient. In this connection the work published by Roles and Todd[6] (1933) throws light on the subject of the prognosis in untreated bronchiectasis. These authors based their statistics on a series of 106 cases of established bronchiectasis which they followed up for from three to six years. They divided their cases into three groups : (1) Dry cases in which the predominant symptom was hæmoptysis. (2) Cases with slight sputum. (3) Cases with copious foul sputum. The first group is frequently thought to be benign but in their series, ten of the fourteen cases had become infected within six years. Of these, three were dead and two totally incapacitated. The second group, those cases with only a little sputum were shown to have a prognosis as bad as those with copious foul sputum. They concluded that bronchiectasis in patients who receive only medical treatment was an extremely fatal disease, for out of forty-nine patients twenty-three were dead and nine totally incapacitated, and of the remainder only four remained "dry" five years after diagnosis. This makes a primary mortality of 47%. An interesting point is, that, of the nineteen patients with septic bronchiectasis who were relatively well, eighteen had been treated by surgery.

I realise that there may be some doctors present who can claim to have followed up a large series of cases of bronchiectasis over long periods who have done perfectly well on a medical regime. Any such series however would be valueless unless there is positive proof of the presence of bronchiectasis as shown by a bronchography.

Such little proof as is obtainable shows, therefore, that bronchiectasis in children and adults is a progressive disease in which a large proportion of cases end fatally.

I should like to point out at this stage that I do not wish to consider, in this paper, the question of bronchiectasis arising from chronic pulmonary tuberculosis or, for example, the transient bronchiectasis seen in cases of septic pneumonitis. It would be best to confine myself to the problem of the classical text book cases of bronchiectasis.

(1) *Age.*—The ideal age for surgery is in childhood *e.g.* between the ages of seven to fourteen. Seven is probably the average lower age limit as very few cases are detected at an earlier age. The upper limit is subject to the problem presented by each individual case. As a general rule, patients over the age of forty may be considered as 'bad risks'. Each subsequent year increases the danger of surgical intervention owing to the toxic offects of chronic pulmonary suppuration on the myocardium.

(2) *Sputum.*—If a very large amount of sputum is being coughed up then this in itself is an obvious indication for surgery. Many of these patients regard themselves as social outcasts and are willing to face any operative risk. A really severe case of bronchiectasis may produce anything upto twenty ounces of sputum a day: this, however, is unusual but surgery must be considered in any patient who is producing over two ounces of foetid sputum a day.

(3) *Hæmoptysis.*—Recurrent hæmoptysis—by that I do not mean the occasional staining present in the chronic bronchitic-bronchiectatic old man—frequently leads us into advising surgery. In my experience, a dry bronchiectasis confined to a midde lobe is a frequent source of recurrent large hæmoptyses.

(4) *Recurrent Pneumonitis.*—Recurrent attacks of pneumonitis in the affected lobe should nearly always be regarded as an indication to resect the affected lobe or its segment. Similarly the patient with progressive general toxæmia resulting from gross bronchiectasis should be subjected to surgery.

(5) *Symptomless Bronchiectasis.*—An interesting problem is that of symptomless bronchiectasis discovered in children. I have already mentioned the findings of Todd and Roles and it should be remembered that only a few children with even symptomless bronchiectasis proceed to travel the normal span of life. Lobectomy in children is a comparative easy technical operation and my own opinion is that all children with bronchiectasis, even symptomless cases, should undergo lobectomy. The problem in children is largely one of diagnosis and I have no hesitation in saying that the child with a 'chronic chest' or the child who is constantly sniffing and coughing should undergo bronchography. Bronchiectasis will often be shown in these children after bronchogram, although the plain film of the chest may be perfectly clear. Admittedly, a large number of these children suffer from a chronic upper respiratory tract infection; nevertheless the co-existence of bronchiectasis cannot be excluded and a good bronchogram will often show bronchiectasis.

Unilateral bronchiectasis is rarely confined to one lobe more often, on the right side the middle and lower lobes are simultaneously affected and, on the left side the *lingula and lower lobes are involved.*

One is occasionally presented with a patient with bilateral bronchiectasis. Bilateral lobectomy is a formidable, but not impossible, operation. Such cases should be judged on individual merits and the decision to operate depends on the general condition of the patient and the severity of the symptoms.

PRE-OPERATIVE PREPARATION.

Unlike many other operative procedures, a patient requires a prolonged course of preparation for lobectomy or pneumonectomy.

Obviously, a patient in the throes of an acute attack of septic pneumonitis as a result of bronchiectasis is not ready for surgery until the acute attack subsides. Similarly, a patient who is coughing up vast quantities of sputum should be prepared by correct postural drainage so that at the time of operation his sputum "output" is at a minimum. If the sputum is unusually foetid then bronchoscopic aspirations with penicillin replacement or aerosol penicillin inhalations will help matters if the organisms infecting the bronchial tree are penicillin sensitive.

OPERATION.

Formerly great stress was laid on the importance of adequate upper lobe adhesions to prevent the upper lobe from "dropping down" after resection of the lower lobe. Modern chemotherapeutic agents and improved methods of bronchial closure have rendered unnecessary artificial pleurodesis of the upper lobe, and most surgeons do not hesitate now to operate in the presence of a free pleural space.

Before commencing operation a drip transfusion is started. A standard lobectomy will require two pints of blood—but in the presence of dense vascular adhesions or a vascular accident up to five pints may be needed urgently.

The operative approach that I employ for a lower lobectomy is through the bed of the sixth or seventh rib. For pneumonectomy I reach the hilum through the bed of the fifth or fourth rib ; whilst the constituents of the hilum of the upper lobe are most accessable through the bed of the fourth rib. The postero-lateral approach is the one that I have always used—even in cases of middle lobe resection.

After the pleura has been opened, the lung or lobe, as the case may be, is freed from the parietal pleura till the hilum is reached. In the case of children, owing to the absence of adhesions, this stage of the operation can be rapidly completed ; in adults, however, when the lung has been exposed to recurrent attacks of pneumonitis, the adhesions may be extremely dense and a partial extrapleural stripping may prove necessary before the hilum can be reached. If lobectomy is contemplated, the interlobar fissure is next defined down to the hilum of the lobe.

The standard technique now employed is one in which the elements of the hilum—that is to say the pulmonary artery, the pulmonary vein and the bronchus—are individually isolated and dealt with. Both the pulmonary artery and vein are frequently thin walled and may be closely adherent to the bronchus. Accidental injury of either vessel will result in torrential hæmorrhage in the depths of the wound ; control of the cut end of the vessel may prove difficult as it may retract into the pericardium. Quite apart from the dangers of hæmorrhage there is the very real danger of air-embolism—which is of course immediately fatal—arising from injury either to the stem pulmonary vein or even one of its smaller branches.

When the pulmonary vessels have been ligated the surgeon proceeds to isolate and close the bronchus. If it is felt that there is a danger of flooding the bronchial tree, during operation, from the secretions of a very "wet" lobe and if intra-bronchial occlusion has not been carried out either with a balloon or tampon before operation, then it is as well to clamp the bronchus, temporarily, as soon as the hilum is exposed. Many methods have been described to ensure a secure and precise closure of the bronchus. It is not possible for me to discuss the details of the subject. Whatever method is employed, one can assume that at some stage of the post-operative period the bronchus will partly spring open; it is imperative, therefore, to cover the bronchial stump with sufficient viable tissue to obviate the dangers of a large broncho-pleural fistula, and to provide adjacent granulation tissue to allow the gradual obliteration of the fistula.

Segmental lobectomy is an elaboration of the procedure that I have just described. The vessels and bronchi of the affected segment are isolated and dealt with individually; the segment is then peeled off the main lobe.

Having completed the operation, any bleeding points which cannot be controlled by ligature are packed with Gelfoam. The chest is flooded with saline to test for a bronchial leak. Pencillin is injected into the pleural cavity. The chest wall is then closed without drainage. After lobectomy the air is completely removed to enable full re-expansion of the remaining lobe. After pneumonectomy, intrapleural pressures are adjusted to atmospheric. In children, and if there has been any soiling of the pleura, an intercostal under-water drain is used.

The patient is bronchoscoped as a routine after operation.

POST-OPERATIVE CARE.

In the absence of cyanosis or a very rapid pulse rate I do not give my patients oxygen.

The post-operative complications of pulmonary resections are similar to those of other operations—*e.g.* shock, post-operative hæmorrhage etc. There are some special complications however, that are peculiar to lobectomy and pneumonectomy:—

(1) *Post-operative lobar or pulmonary collapse.*—This calls for immediate bronchoscopy to clear the bronchi of retained secretions; if necessary, bronchoscopy can be carried out with the patient sitting up in bed. I have performed probably over a thousand bronchoscopies for various conditions other than following lobectomy or pneumonectomy and I have come to the conclusion that the thoracic surgeon (and his resident staff) should be completely 'at home' with the bronchoscope. Many lives can be saved by the prompt use of the bronchoscope. On a number of occasions I have demonstrated, on the X-ray screen, immediate re-expansion of a collapsed lobe or lung after bronchoscopy.

(2) *Bronchopleural fistula.*—Between the tenth and fifteenth days the bronchial sutures almost invariably give-way and a small leak occurs. If sufficient tissue has been used to cover the bronchial stump the opening will close rapidly. Some cases pass on to form a small, loculated empyema. Such an empyema can be controlled by aspiration and pencillin replacement—but a few will require rib resection and drainage for a short period. A broncho-pleural fistula and pleural infection is of lesser importance after lobectomy than after pneumonectomy. After pneumonectomy, in the presence of a persistent broncho-pleural fistula, thoracoplasty, with or without a muscle graft to the bronchial stump, is usually necessary.

I endeavour to persuade my patients to sit out of bed forty-eight hours after operation. They are usually fit for discharge from hospital in three to four weeks.

CASES OF LUNG RESECTION FOR BRONCHIECTASIS.

Lobectomy—12 cases.
Segmental Lobectomy—4 cases.
Pneumonectomy—2 cases.
Operative mortality—nil.

Two patients developed small bronchial leaks which healed spontaneously. One patient developed an ipsi-lateral lobar collapse which re-expanded after bronchoscopy. No patient developed an empyema or needed drainage or thoracoplasty.

In conclusion, I should like to say that the success of any intrathoracic surgery depends on team-work. Anyone of us can present the occasional successful case—but to present persistently good results over a large series of cases we have to develop a thoracic team consisting of a physician, surgeon, anæsthetist, resident doctors, and (a very important point) the sisters and nursing staff. To develop a team of this nature, which can work in perfect harmony, may take a year or even years; but it is only through such team-work that we can ever hope to achieve good results in major intra-thoracic surgery.

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RESECTION OF THE RECTUM FOR CANCER WITHOUT AN ABDOMINAL COLOSTOMY

E. J. Borges*

If there is one thing that makes a patient of cancer of the rectum hesitate to undergo a radical operation for his disease, it is the prospect of going through life with all the horrors which he imagines are associated with an abdominal colostomy. All references to other patients who have undergone the ordeal and are living happy contented lives despite their colostomy are accepted with a shrug of the shoulders and a muttered statement to the effect that all cannot be heroes. After much persuasion and exposition of the bleak outlook without an operation, many accept the colostomy as inevitable and reluctantly consent to the procedure in despair. Some refuse to consider the operation at all and seek counsel elsewhere, often to return penitently after some months in a hopelessly inoperable condition.

Yet, it is a curious fact that to those who have an abdominal colostomy after a radical resection of the rectum, the presence of this abnormal anus is not the trial of the flesh that most people think it must be. In our experience all these patients at first accepted the colostomy with resignation, but after the first few months, when they had learned to regulate their bowels, they all have expressed surprise that the colostomy was not the nuisance they had expected it would be; at the worst it was an inconvenience that they could well put up with. A few did not mind it at all, among them a doctor working in a railway hospital who periodically writes to say that his colostomy gives him no trouble and that it does not interfere with his hospital duties.

Now, all these contented people do not go about advertising their colostomy. They would rather not draw attention to a defect of which people are unaware. But the patient who has a palliative colostomy for an inoperable cancer is loud in exhibiting his woe, because, apart from the unnatural discharge of faeces, he also has pain, tenesmus, and discharge of blood and mucus associated with an advancing growth in the rectum. With all the unreasonableness of a chronic sufferer he is even inclined to blame the colostomy, and the surgeon who inflicted it on him, for his plight. And so a general impression is created on the layman and even the general practitioner that a colostomy life is hell on earth.

As long as surgery remains the only certain way of treating rectal cancer, the maximum assurance against recurrence is only provided by the widest possible dissection of the lymphatic field. If this cannot be achieved unless a colostomy becomes an essential feature of the operation one is justified in demanding from the patient the supreme sacrifice of his rectal sphincters. But is there sufficient evidence to uphold such a contention? That is the question which is in the minds of many surgeons today.

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The operation that has been so far universally accepted as the most radical, and as giving the highest percentage of cures, is resection of the rectum and its lymphatics through a combined abdominal and perineal approach. It may be done in one or two stages. Our preference is for the Miles operation of abdomino-perineal resection in one-stage, in which the abdominal part is done first, a colostomy established, and the perineal part follows immediately, the isolated rectal specimen being removed from below. It used to be considered a very formidable operation in this country with a prohibitive mortality in the Indian subject, but, with modern advances in pre- and post-operative care and with increasing experience of major surgical problems the operation has lost its terrors. At this hospital, of the 36 radical rectal resections done upto the middle of 1948 with a mortality of 3, only one death occured among the 16 patients subjected to the one-stage abdomino-perineal resection—a mortality of 6.3%. The cause of the death in this one case was uraemia on the 9th day. The results of these radical procedures have been very satisfactory.

Indeed, the results in rectal cancer to-day are some of the best in the whole field of cancer treatment. There was a time in the late years of the last century when restricted excisions were done through a perineal or trans-sacral approach (the Kraske and other operations). The recurrences were many, and surgeons progressively devised operations that extirpated wider and still wider fields of tissue in their attempts to eradicate all possible areas of spread. Miles[7] with his description of the abdomino-perineal operation in 1907 achieved the most radical operation of them all, and reduced the recurrence rate to a lower level than it had ever reached before. But the pendulum to-day appears to be swinging back, and an increasing number of surgeons are practising and advocating less radical procedures with, saving of the sphincter mechanism in selected cases.

The question that naturally arises is: Are we not putting the clock back in practising these restricted resections and running the risk of an increase in the recurrence rate? The older surgeons, *e.g.* Frank Lahey[8] and Thomas Jones[8] who have lived through the evolution of rectal surgery are convinced that this new tendency is bound to end in a rise in the recurrence rate, and fall in the 5-year cure rate. What have the advocates of the less extensive procedures to say to this? They bring sentimental, anatomical and statistical evidence to their support.

There is no doubt that a small percentage of patients, some of them early curable cases, refuse a radical operation because of the colostomy associated with it. These cases are lost and could be saved if a sphincter saving operation could be proposed to them.

The radical operation of Miles was based on his conception of the spread of cancer along the anatomic lymphatic pathways of the rectum described by Cuneo, etc. When pathological studies were made of the spread of cancer in resected specimens, and in post-mortem subjects, it became increasingly clear that the main stream of spread of cancer cells was upwards, from lymph node to lymph node, along the lymphatics accompanying the superior haemorrhoidal vessels [3], [4], [5], [11]; spread outwards or downwards occurred less frequently, and then only when a large number of lymph nodes were blocked along the upward route. In fact in a collected series of 507 resected and post-mortem specimens examined by Westhuer,[11] McVay,[6] Wood and Wilkie,[12] Gabriel *et alia*,[4] Gilchrist and David,[5] Coller *et alia*,[3] in only 8 cases were any involved lymph nodes found below the site of the lesion in the rectum (Waugh).[10] From this it may be concluded that in the average operable case any operation that extirpates the ascending lymphatic field together with the cancer is radical enough for practical purposes, and in many cases there is no necessity to sacrifice the sphincters or more bowel than that deprived of its blood supply.

Another anatomical feature that has deterred surgeons from attempting anterior resections and anastomosis for rectal lesions has been the traditional teaching regarding the "critical point of Sudek", and the precarious blood supply of the organ after ligation of the inferior mesenteric artery. This anatomical myth has been exploded in recent times. It has been shown that the rectal stump does survive even if the only source of supply is the inferior hæmorrhoidal vessels.[2] Therefore, there is no danger in ligating the inferior mesenteric artery at any point provided at the time of anastomosis the anastomotic edges of bowel are seen to be adequately supplied by blood.

This better understanding of the lymphatic and vascular anatomy of the rectum has been mainly responsible for the swing towards conservative resections noticed in these days.

Ultimately, the question whether the less radical operations are justifiable or not can only be answered by a study of the end-results. Until recently not many figures were available of long term follow up studies after these operations. But now, both Dixon and Wangensteen, two of the most ardent advocates of these procedures, have published results which make very interesting reading.

Wangensteen[9] has reported 63 cases of cancer of the rectum and recto-sigmoid treated by anterior resection and anastomosis. Local recurrences in these cases occurred in 14 of the cases and were distributed as follows: Where the growth was situated below 5 cm. from the anus there were 2 recurrences in 7 cases (30%); between 6 to 8 cm. from anus—

3 recurrences in 12 cases (25%); between 9 to 13 cm. from anus—2 recurrences in 32 cases (6.3%); between 14 to 20 cm. from anus—no recurrence in 20 cases (0%). From this it appears that in the group of cancers situated more than 9 cm. from the anus the chances of a recurrence are minimal, and the operation would appear to be justified. However, a closer study of Wangensteen's figures dispels the optimism first created. All these cases were treated after 1942 and only 10 were operated on more than 5 years before Wangensteen's report. Also of the 12 cases in the 14 to 20 cms. group in whom no local recurrence was noticed, 7 cases were done after 1945, *i.e.* less than 2 years before Wangeensten's report was made. Presumably if all these cases are followed for five years many more local recurrences will appear. Nevertheless, one may conclude that the chances of recurrence in the cancers situated higher up in the rectum are comparatively smaller, and therefore conservative operations in this situation may be justified.

Dixon's figures for 5-year cure have recently been given by Waugh.[10] In 272 cases of cancer situated 6 cms. from the anus and above, the 5 year cure rate was 67.7% (74% in 150 cases without node involvement and 58% in 122 cases with node involvement), results that compare favourably with the Miles operation. In fact, the figures are so good that one is inclined to believe that a certain amount of selection of cases for anastomosis must have occurred, the more advanced cases having been treated by an abdominoperineal resection with colostomy.

From the results of Wangeensteen and Dixon quoted above it is clear that at least in *selected* cases of cancer situated above 9 cms. from the anus the operation of anterior resection with anastomoses may be done with chances of a 5-year cure almost equal to those of more radical surgery. Until the results of other surgeons with the operation are forthcoming, however, unqualified approval cannot be given to these conservative procedures.

We, at the Tata Memorial Hospital, have so far advocated and practised the one stage abdomino-perineal operation of Miles as being the most satisfactory operation in rectal cancer. But in view of the considerations discussed above we have now decided to give a trial to the conservative operations within the limits set out before. The first case of anterior resection done is recorded below:

Case No. H 678.—A 57 year old man with a history of passing blood and mucus in the stools for 4 months was seen in March 1948. Rectal palpation revealed a growth situated in the anterior wall of the rectum about 3 inches from the anal margin. The rectal wall at this point could be moved with the growth. The upper limit of the lesion was beyond the reach of the finger. Proctoscopy revealed a cauliflower-like tumour in the anterior rectal wall 3½ inches up, which could be pushed upwards to 5½ inches indicating a partial prolapse. The upper limit of the lesion was 7½ inches from the anal verge. Biopsy proved a colloid cancer.

As the patient was averse to a colostomy and as the growth was situated in the upper rectum it was proposed to try a resection with end-to-end anastomosis if possible. A laparotomy on 23-3-48 revealed an intussusception of a rectosigmoid growth into the mid-rectum. There were no palpable lymph nodes or any evidence of abdominal metastases. An attempt to reduce the intussusception showed that the growth was about to burst through the bowel wall and so the attempt was given up. The lower rectum was mobilised sufficiently to permit an adequate stump for a low pelvic anastomosis. The intussusception was resected with the adjacent thickened mesentery. End-to-end anastomosis between the lower sigmoid and the stump of rectum was completed between clamps. The anastomosis was placed extraperitoneally in the pelvic cavity and the abdomen closed without a colostomy. A small perineal incision in front of the coccyx was used to insert a rubber drainage tube upto the anastomotic site. A rectal tube was stitched in and the patient returned to the ward.

The resected specimen measured 15 cms. in length after reduction of the intussusception. A cauliflower growth measuring 8 cms. in length occupied the middle portion of the specimen almost surrounding the lumen, and infiltrating right through the bowel wall. The cut surface looked gelatinous. There were six enlarged and firm lymph nodes in the pararectal tissue which appeared to be involved with cancer. Histological examination revealed a colloid cancer of the rectum, but the lymph nodes only showed sinus catarrh with no metastatic deposits.

There were no post-operative complications. The abdominal wound healed primarily. A stool was passed through the rectal tube after 48 hours. The tube was removed on the 5th day after which the bowels moved naturally. The drainage tube was removed on the same day, there was no discharge and the perineal wound healed by granulation in a few days. The patient was discharged on the 15th day quite well A letter received recently one year after operation states that he is well and is having normal bowel movements.

The result in this case is most gratifying. The post-operative course, the short period of hospitalisation, and above all the absence of a colostomy made the operation most acceptable to the patient as well as to the nurses and house surgeons on whom the burden of managing the colostomy always falls. Because of all this the operation is most attractive. It remains to be seen if it also gives a reasonable immunity from recurrence. Only time will tell.

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MEDICAL PROGRESS

CASEIN HYDROLYSATE—ITS USE IN THE LABORATORY AND THERAPEUTICS§

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The word hydrolysate has come into prominence only recently but the meaning it conveys, namely "the end product of hydrolysis," is not new. The homely word "digest" conveyed about the same meaning but not so accurately. In the chemical laboratory engaged in the study of amino-acids or protein chemistry in general, the hydrolysis of proteins has been carried on as a routine method for more than a hundred years.

In the bacteriological laboratory, peptone has been used for more than sixty years following the researches of Loeffler (1881). The word peptone, even now, conveys to the mind of the bacteriologist the meaning "hydrolysed protein" but the protein understood is either mutton or beef or some by-product of the slaughter house.

Cole and Onslow (1916) were probably the first to use casein hydrolysate as a bacteriological medium. This was in England, under the stress of the first World War, when foreign-made peptone was not available and meat was very scarce. This hydrolysis was carried out by means of pancreatic extract. Although this work was carried out under the auspices of the Medical Research Council, this medium does not seem to have been used on a large-scale even in England. The acid hydrolysis of casein is of more recent origin.

Ever since the days of Haffkine, the Haffkine Institue had been using an acid hydrolysate of mutton as a bacteriological medium for the preparation of plague vaccine. This medium had certain limitations. Mutton is, after all, a very variable commodity, in Bombay especially. But the most important drawback of the medium was that the hydrolysis was not complete. About 20-30% of the protein was left unhydrolyzed and went as such into the final medium. It was noticed that vaccines made from an incomplete hydrolysate gave more reaction than those made from a complete hydrolysate. This was one of the considerations that influenced the Institute to change over to casein hydrolysate.

Before considering the merits of casein hydrolysate as a medium for making vaccines, it would be appropriate to give a description of the method followed at the Haffkine Institute for the preparation of this medium. Each charge is of 150 litres and is made up as follows :—

Water	130 litres.
Acid sulphuric, B. P.	7.2 l.
Acid Hydrochloric, B. P.	5.2 l.
Casein	15 kg.

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The concentration of sulphuric acid thus obtained is about 1.8 Normal. The hydrochloric acid serves not so much as an hydrolyzing agent but contributes sodium chloride to the finished hydrolysate. The mixture is boiled in a steam jacketed glass-lined kettle fitted with an enamelled stirrer and thermometer well and also a reflux condenser. The steam inlet is so regulated that the temperature remains between 101°—102°C. and a gentle refluxing goes on as seen through the glass condenser. This refluxing is continued for 48 hours at a stretch. After digestion the liquid is allowed to cool down to about 80°C. and then run into another glass-lined open kettle fitted with a glass-coated agitator. Here it is neutralized slowly with barium carbonate. The neutralization is carried on till a test filtrate shows only a trace of sulphate and absence of barium. This is necessary as barium is bactericidal and vaccines containing barium salts in solution would be harmful. The mass is filtered through a filter press using cloth as the filtering medium. The yield is about 70-75%. The concentrated hydrolysate is kept in glass carboys in cold storage till required. For making the medium, one volume of the concentrated hydrolysate is diluted with one volume of water and boiled for half an hour with 0.5% activated charcoal (Muchar C-190). After boiling, the liquid is filtered through a filter press using a specially prepared filter paper as the filtering medium. The clear fluid is neutralized with 0.5 N caustic soda. The reaction is adjusted to about pH 7.5-7.55. The same quantity of charcoal as used before is again added, the liquid brought to the boil and again filtered through the same filter press but using fresh set of filter papers. At this stage, the total nitrogen of the filtrate is determined. The volume of the concentrated hydrolysate is measured and distilled water added so that the final hydrolysate should contain 270 mg. total nitrogen per 100 ml. The reaction is adjusted to pH 7.4—7.45. No sodium chloride is added to this medium as the hydrochloric acid used in the hydrolysis when neutralized with caustic soda provides about 0.5—0.55% sodium chloride. The initial charge of 150 litres gives about 400 litres of finished hydrolysate.

At the Haffkine Institute the primary consideration for changing over to casein hydrolysate as a medium for making vaccines was that it was a much better medium than any we had used before. Using the method of Sokhey (1939) for determining the number of viable plague organisms in broth culture we used to get about 180—220 million organisms per ml. when grown in acid digest broth. With casein hydrolysate we get 800—1000 million organisms, that is, about four times more.

The second consideration for adopting casein hydrolysate as the medium of choice for the preparation of plague and cholera vaccines is that it is a complete hydrolysate. No protein or proteoses are left unhydrolyzed. The hydrolyzing time limit of 48 hours was decided upon because it was found by several trials that the hydrolysis was complete by about 45 hours. This was ascertained by determining the total nitrogen of a sample as such and of another sample which had been saturated with sodium sulphate to precipitate the unhydrolyzed proteins or proteoses. When the two determinations agreed within the limits of experimental error the hydrolysis was considered to be complete. The acid hydrolysate of mutton contained about 20-30% unhydrolyzed proteins as mentioned above. This hydrolysate was more toxic than casein hydrolysate to laboratory animals. Casein hydrolysate, when tested intradermally on human volunteers, gave no reaction. The vaccines made from casein hydrolysate are less toxic than those made from the acid digest of mutton. The ratio is about 1 : 4 (Sokhey 1944). The mouse protective dose for vaccines made from the two media is in the ratio of 1 : 2.5. Putting all these figures together casein hydrolysate may be said to be ten times superior to the acid digest of mutton.

The method outlined above is essentially the method of Mueller and Johnson (1941). The main difference is the time of hydrolysis. Mueller recommended 72 hours.

The disadvantages of the sulphuric acid method of hydrolysis are the time taken to neutralize the acid with barium carbonate and the large amount of barium sulphate precipitate. Barium carbonate is cheaper than barium hydroxide but the latter is more convenient to use. With the former the carbon dioxide evolved is a nuisance and the neutralization is necessarily very slow as the fluid rises. Barium hydroxide neutralizes the charge very rapidly as the fluid does not rise and there are no unpleasant sensations associated with its use. Barium hydroxide carries with it eight molecules of water of crystallization and that increases the volume of the charge by 15% which is a draw-a-back.

To avoid the difficulty of neutralizing sulphuric acid and removing the barium sulphate precipitate, hydrochloric acid can be used as the hydrolyzing agent. Mueller (loc. cit.) describes a method. After hydrolysis, the excess acid is removed by distillation under vacuum, but much remains behind and has to be removed by a laborious chemical process.

Hydrolysis of proteins by sulphuric or hydrochloric acids leads to the destruction of tryptophane and the possible dismutation of a certain amount of cystine, serine and threonine. Most proteins when boiled with either of these strong catalytic agents yield a black or brownish black substance called humin. The loss of tryptophane can be made up by adding synthetic tryptophane. Gladstone and Fildes (1940) overcome the difficulty by mixing an acid digest of casein with a tryptic digest. Incidentally, their medium is further fortified with yeast, sodium glycerophosphate, glutamine and sodium lactate.

The whole question of the hydrolysis of proteins has received a sudden impetus in recent years because of the parenteral use of protein hydrolysates. This is within the last ten years. The early animal experiments were performed with acid hydrolysate of casein. The first trial of parenteral administration of protein hydrolysate on human beings, that of Elman and Weiner (1939) was with an acid hydrolysate of casein fortified with tryptophane and cystine.

Parenamine, manufactured by F. Stearns & Co. is an acid digest of casein prepared according to the method of Sahyun (1941). The product has been favourably reported in clinical trials by Kozoll, Hoffmann and Mayer (1945) and the changes in the blood chemistry have also been reported by Hoffmann, Kozoll and Osgood (1946). Sahyun's method differs from Mueller's in that the sulphuric acid used is 5N and instead of refluxing, the hydrolysis is carried out under a pressure of 15 lbs. for 16 hours. Of course, tryptophane is destroyed and this amine acid is separately added to the finished hydrolysate. In this connection it is interesting to note that this preparation is sold as a 15% protein solution. This high concentration of protein is obtained by concentrating the finished hydrolysate *in vacuo* till the necessary concentration is reached.

The loss of tryptophane can be avoided at least to some extent by reducing the time of hydrolysis. Whereas, for bacteriological media it is imperative that the hydrolysis be carried to completion, this drastic treatment is not necessary for hydrolysates meant for parenteral use. In fact it is advantageous not to carry the hydrolysis to completion as it has been repeatedly demonstrated that incomplete hydrolysates give better results clinically than mixtures of amino acids. White and Sayers (1945) using different concentrations of sulphuric acid and varying the period of hydrolysis have proved that it is possible to prepare an incomplete hydrolysate of casein by acid hydrolysis without losing much of the tryptophane. It is necessary to hydrolyze the protein to that extent only where it will lose its immunological and toxic properties. Mukerji (1945) and Iyengar, Biswas and Mukerji (1946) have shown that the protein hydrolysate prepared by them does not give a precipitate either with 5% trichloroacetic acid or with a saturated solution of picric acid, thereby showing absence of both primary and secondary proteoses. But the ratio of amino nitrogen to total nitrogen is only 30% showing that it is an incomplete hydrolysate. With a complete hydrolysate this ratio should be about 70%.

The method used at the Haffkine Institute for the preparation of casein hydrolysate for parenteral use is based on the work of White and Sayers. This is similar to the method used for the preparation of the bacteriological medium described above, except that the sulphuric acid used is 2.6 N and the time of hydrolysis only six hours. Hydrochloric acid is added after hydrolysis. The hydrolysis is not carried to completion thereby saving total destruction of tryptophane. By actual analysis we have found that about 40% of tryptophane is destroyed by this method.

The same glass-lined equipment and filter-presses as used for the preparation of the bacteriological medium, are used. But all equipment is thoroughly washed and finally rinsed with pyrogen-free distilled water before use. The filter cloths are boiled in pyrogen-free distilled water. After neutralizing the sulphuric acid with barium carbonate, the liquid is boiled with 0.5% activated charcoal, filtered and neutralized with 10 N caustic soda. The reaction is adjusted to pH 7.2. The same quantity of charcoal as used at first is again added and the liquid brought to the boil and filtered. Nitrogen is determined and the liquid diluted with pyrogen-free distilled water. The liquid is again filtered through Buchner funnels and also through sintered glass funnels, measured into bottles and sterilized at 115°C. for 15 minutes. The final dilution of the hydrolysate is so arranged that the finished product should contain 0.75-0.8% total nitrogen which is the equivalent of 5% protein. The ratio of amino nitrogen (Sorensen) to total nitrogen is slightly more than 30%. The sodium chloride concentration is between 0.85-0.9%.

The hydrolysate is supplied in bottles containing 400 ml. Another bottle containing 100 ml. of 25% glucose is also supplied with instructions to mix the two before injecting. It is necessary to supply the two solutions separately as the hydrolysate, which is light brown in colour, deepens in colour on adding glucose and after sterilizing turns dark brown. In fact the colour is so dark that it is not possible to examine the bottle for floating particles. This is due to the formation of melanin-like compounds by the interaction of tryptophane and glucose. This reaction goes on even during storage and renders the hydrolysate less and less useful.

Each batch of parenteral casein hydrolysate is tested in rabbits for pyrogen. Rabbits weighing between 1500 gms. and 2000 gms. are kept in an air conditioned room. Their normal temperatures are determined and only those rabbits are used for the tests whose normal temperatures fall within 102.0°F and 103.6°F. Five rabbits are used for each test. 10 ml. of the test solution per kilo of body weight is injected in the ear vein of each rabbit and rectal temperatures taken every hour for three hours. A rise of 1.08°F is taken as evidence of pyrogen.

From the point of view of pyrogen the method of acid hydrolysis is superior to other methods of hydrolysis as the acid destroys any pyrogen that may be present in the raw materials, whereas with other methods the pyrogens of the raw materials remain in the hydrolysate and are almost impossible to remove as will be seen later. Besides, the method is almost continuous and undue exposure is avoided thereby preventing gross contamination. Traces of pyrogen that may have been introduced during the process after hydrolysis are removed by the two filtrations with activated charcoal.

In the preparation of protein hydrolysate for parenteral use the emphasis on tryptophane is due to the work of Elman (1938) who showed that only when tryptophane and cystine were added to an acid hydrolysate of casein—a complete hydrolysate—did positive nitrogen balance occur. Conversely as soon as the two amino acids were omitted, the animal went into negative nitrogen balance. In later experiments, Elman (1939) injected the tryptophane and cystine six hours after the injection of the unsupplemented acid hydrolysate. Even such a short delay resulted in negative nitrogen balance. This has been confirmed on human beings also.

There are many protein hydrolysates on the market. The most popular among these is Amigen, made by Mead Johnson & Co. This is a tryptic digest of casein. Enzymic hydrolysates of casein and other proteins are more popular than acid hydrolysates. With enzymes, hydrolysis cannot be carried to completion. With trypsin, the maximum hydrolysis that can be reached is 60%. With papain it is still less. The enzyme of choice in foreign countries is trypsin. It is used as such or in the form of pancreatic extract. In this country, papain seems to be more popular. The protein hydrolysate used by Krishnan (1944) in the Bengal famine of 1943-44 was a papain digest of pork. A papain hydrolysate of casein made by Eli Lily & Co., has been favourably reported upon (Whipple 1941). Capain is another papain hydrolysate of casein. (Brinkmann *et al.* 1945). With enzymic methods the risk of bacterial contamination and hence of pyrogen, is very great. The makers of Amigen have also had difficulties in the beginning. Shohl (1939) reported severe reactions with Amigen. Elman (1940) also reported reactions. It was only in 1942 that favourable reports began. The makers have evidently improved the technic very much as they have been granted a patent, (Kemmerer 1941.) The advantage of papain over trypsin is that the optimum temperature of hydrolysis with this enzyme is 55°C, whereas with trypsin it is 40°C. Hence the risk of microbial contamination is much less. The disadvantage in the use of papain is the very large quantity of the enzyme required for optimum digestion. Krishnan (loc. cit.) has used 17-50 gms. of papain per kilo of pork used.

Although casein is the protein of choice in the manufacture of protein hydrolysate for parenteral use, other proteins have also been used. Pork has been mentioned above. Skimmed milk, mutton, beaf, liver and other organs and mixtures of two or more sources of protein have been tried with varying success.

In the preparation of protein hydrolysate the greatest difficulty is the contamination with pyrogens. Co Tui's method (1937) of removing pyrogens by adsorptive filtration through seitz filter pads is not applicable to protein hydrolysate which is a colloid. Zittle (1945) using the same method of adsorptive filtration came to the conclusion that the quantitative removal of small amounts of pyrogen from complete hydrolysates is feasible but their removal from partial hydrolysates is impractical. There is a limit to the adsorptive capacity of the filter pad. One square centimeter of filter pad can adsorb about 10 micrograms of pyrogen from an aqueous solution but for the same quantity of pyrogen added to an incomplete hydrolysate the filter area must be twenty times as much. Such large filtering areas would adsorb amino acids more then pyrogens and that would detract from the value of the hydrolysate. Smith and Penell (1947) have succeeded in removing pyrogen from solutions of haemoglobin and plasma by filtration through a different type of filtering pad (S_6) or by using an adsorptive agent Decalso. We have found the S_6 pad to be a failure. These authors have confirmed the findings of Zittle that there is a relationship between the degree of pyrogenicity and square area of filter pad required to remove it. Wretlind (1946) has succeeded in removing pyrogens from an enzymic hydrolysate of casein by dialysis. This seems to be strange. Many of the amino acids would pass out of the dialyzing bag and would thus be lost. Another question which arises is whether pyrogens would pass through a semi-permeable membrane. Co Tui (loc. cit.) has come to the conclusion that the molecule of pyrogen is of a size between 50 millimicrons and one micron. If this is true, it is doubtful if a particle of this size will pass through a dialyzing bag. This method has not been tried at the Haffkine Institute as there are no facilities at present for producing the large quantities of pyrogen-free distilled water that would be required for the dialysis.

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MEDICAL PRACTICE

DIAGNOSIS AND TREATMENT OF CHANCROID *

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Immediate diagnosis of a chancroid or a soft sore by a clinical examination is impracticable. It is dangerous and at times disastrous. Diagnosis of a chancroid is arrived at by a process of exclusion and it usually takes a period of three months, which is required to exclude the possibility of syphilitic infection. In the meantime, a genital ulcer or ulcers are labelled as N.Y.D.V.S. (not yet diagnosed venereal sore), and investigations are carried out for the accurate diagnosis. Venereal sores are given topical application of normal or hypertonic saline and are subjected repeatedly to darkfield examinations for *Tr. pallidum* for three days. Patients are given, as a routine, two tablets of sulphathiozol O.SG. each, four to five times a day, at four hourly intervals, and copious fluids to assure normal output of urine. Blood is taken at regular intervals for serologic tests for syphilis till three months' period has elapsed for that is the incubation time for syphilis. In chancroids, incubation period of one to three days, superficiality and multiplicity of lesions, undermined and irregular edge, loss of tissue, painfulness, tendency to bleed easily, absence of induration, enlarged, tender and painful inguinal lymph glands etc. are points of some value but they are not always available and are often subjected to alteration by the presence of other factors; hence they are not of material help in reaching an early diagnosis. They allow only of "presumptive diagnosis" but a definite opinion could never be expressed in any case until the twelfth week has been reached. The diagnosis of chancroid is usually based on negative results of darkfield examinations for *Tr. pallidum*, clinical improvement following trial of sulpha drugs and continued negativity of serologic tests for syphilis Skin tests (Auto-inoculation and Reinstierna's test of intracutaneous injection of 0.2 c.c. of the dead suspension of Ducrey bacillus) and smears do not yield a positive diagnosis. In an effort to establish more valid criteria for identification of the disease, Heyman, Beason and Sheldon[1] compared various diagnostic methods in 125 cases and a diagnosis of chancroid was established in 60 cases by culture, by biopsy or by both methods. Though non-specific, microscopic changes in chanroid have a histological pattern so constant that biopsy appears to be the most. efficient single diagnostic procedure. A histologic diagnosis of chancroid was made in 45 of 59 cases in which biopsy was done and was confirmed by culture in 35 cases. A 3 mm. fragment of tissue from the ulcer is taken with a Gaylors forceps and the examination of sections shows three distinct zones. The surface zone or the base of the ulcer is shallow, consisting of polymorphonuclear leucocytes, fibrin, red blood cells and necrotic tissue. Below this is a fairly wide layer of edematous tissue containing chiefly endothelial cells in various stages of proliferation, many newly-formed blood vessels showing palisading and an occasional area of degeneration or thrombosis. Finally, the deeper zone shows dense infiltration by plasma cells and lymphocytes. Ducrey bacilli are at times seen. Biopsy is feasible and efficient in more advanced lesions, in which cultures or smears give poor results.

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In cases of small early primary lesions, diagnosis by culture and smear is most likely to be successful. Cultures are made of all genital lesions or aspirated material from buboes on whole defibrinated rabbit blood media, and the stained smears made from the cultures after 24 to 48 hours' incubation, are examined for Ducrey bacillus. This procedure revealed Ducrey organisms in 50 cases. Old and secondarily infected lesions often give negative cultures and smears.

Skin testing with Ducrey vaccine is of limited value. It becomes positive after about eight days of infection and remains so indefinitely. The validity of skin tests is diminished by the persistence of cutaneous hypersensitivity for years the after acute infection. One cannot be certain, therefore, whether a positive test represents the existing infection or a previous one. Positive skin tests were found in only 46 of the 60 proved cases of chancroid thus giving a percentage rate of 77.

Autoinoculation yielded 20 positive cases in 36 of the 60 proved cases of chancroid. A loopful of exudate is rubbed into a scarified area on the patient's arm, and the area is kept covered for 48 hours. A positive reaction is shown by an appearance of small pustules or ulcers in which Ducrey bacilli could be identified and cultured from the autoinoculations. This procedure has several disadvantages and has a limited value as a method of diagnosis. Hence it cannot be recommended for general use. Besides, such a procedure is bound to cause some delay in the institution of treatment.

Smears were positive in 50% of the cases. Diagnosis of chancroid by means of direct smears is based on certain characteristics of morphology, staining and arrangement of bacilli. Positive smears usually show only a few organisms particularly in early cases. In advanced cases especially in women identification is well nigh impossible. Ducrey bacilli are characteristically short, plump, gram-negative bacilli with rounded ends, with a "closed safety pin" appearance in Pappenheim preparations due to bipolar staining. They are sometimes intracellular but more often seen outside the cells, singly or in clusters. At times alignment in long chains is noted.

Although no one method is applicable in all instances, a chancroid can be diagnosed by proper combination of diagnostic procedures in a high percentage of cases. Small early primary lesions should be submitted for culture and smear examinations. This is most likely to be helpful. In advanced lesions, biopsy and section examinations seem to be most effective. The importance of negative darkfield examination for *Tr. pallidum* and negative serologic test need not be stressed.

TREATMENT

Rest in bed is to be preferred specially where the lesion has a tendency to spread and give rise to adenitis or become phagedenous. Topical application of saline to the chancroid is both effective and useful ; it not only aids healing but also facilitates detection of *Tr. pallida,* and early diagnosis of syphilis. Experience has proved the usefulness of administration of sulphathiozole 20 to 25 gms. in five days in chancroids, and 28 to 35 gms. in seven days in cases where buboes co-exist. Routine administration of sulphathiozole helps the lesion to heal more quickly, lessens the chances of inguinal adenitis, and reduces considerably average duration of illness and hospitalization. Local pain and tension in adenitis are relieved by frequent application of dry heat to the groin. Softened buboes are aspirated if necessary often. Incision is contra-indicated. Occasionally, 1, 2 or 3 intravenous injections of chancroid or T.A.B. (1 in 20) Vaccine, on alternate days, ½ to 2 cc, according to the individual reaction come handy in stimulating and accelerating the process of resolution and healing. Penicillin either locally or parenterally must not be used as it is likely to mask early signs of syphilis and make early dignosis difficult or impossible.

POST-TREATMENT SURVEILLENCE—all cases should have serologic tests for syphilis at regular intervals over a period of three months. Quantitative methods of serum testing are to be preferred. Rise in the titre of the reaction suggests the presence of syphilis.

REFERENCE.

1. Albert Heyman, Paul B. Beenson and Walter H. Sheldon: Dignosis of Chancroid. J. A. M. A. 129 : 925-938, 1945.

CURRENT MEDICAL LITERATURE
MEDICINE

MODERN TREATMENT OF EDEMA. GEORGE R. HERRMAN, JOHN W. CHISS, MILTON R. HEZTMANCIK AND PAUL M. SIMS JR. American Practitioner, Vol. 3 : 393-398, 1949.

In this article a resumé of the current status of the treatment of edema with, special attention to cardiac edema and the use of the new mercurial diuretic Thiomerin, has been described. In the treatment of congestive cardiac failure, the reduction of the circulatory load can be accomplished by the following (1) optimum physical rest (2) trapping the blood in the periphery (3) phlebotomy (4) removal of pleural, pericardial, and peritoneal fluid accumulations, which embarass respiration and circulation (5) improvement of cardiac tone by digitalis (6) low sodium, neutral ash and acid salts intake (7) use of mercurial diuretics.

In the modern dietetic treatment of edema, the significance of disturbed electrolyte balance has been well recognised. Many edematous patients react favourably to reduction from 5 to 10 G of sodium chloride to 1½ G to 2 G daily. The adequate protein intake of 1 Gram. per Kilo would supply a minimum of 4 G of salt. The Karell diet treatment with its low salt, low fluid, low calorie, low protein and low fat regime has not met with much success. Scheme reduced the salt intake to 2 G daily with forced fluid intake upto 6 to 8 litres per day. The imbalance that resulted produced diuresis but a concomitant increase in theoutput of sodium has been questioned.

Kuth *et al.* and Gamble *et al.* orally administered 6 to 8 G. of amonium chloride which upset the acid-base equilibrium toward the acid side and altered the osmotic pressure in the intracellular fluids by shift of ions. This heavy dosage, however, produced a severe renal overload and hepatic depression. Shermn suggested dilute hydrochloric acid USP 10%, 0.5 cc. in 200 cc. of H_2O (10 cc. of this acid is equivalent to 1.4 Gm. of ammonium chloride or nitrate).

These authors have tried mercapto mercurial, MT 6 given the trade name of Thiomerin, which is 160 times less toxic than other mercurial diuretics. It was administered to 200 patients sub-cutaneously and to 50 patients intravenously. These suffered from congestive heart failure, oedema due to various causes, cirrhosis of liver, and some from glomerulonephrites. The drug was given in 0.5 cc., 1 cc., and 2 cc. doses, 1 to 15 times, in various patients, at intervals of 5 to 7 days, for as long as 9 months, or daily upto 5 days in succession, without producing any renal or cardiac irritation or any complication. In no patient has any serious toxic reaction such as pain in chest, palpitation, dyspnæa, cyanosis, fainting and collapse, convulsions or death, been reported. Even 2 cc. (80 mg.) has been injected subcutaneously daily for 5 days without toxic reactions.

In 20 patients with a chronic congestive heart failure of various types. Schwab observed that small doses of Theomerin were effective when ammonium-chloride was administered orally. With 0.5 cc. Thiomerin the 24 hour urinary output was 3,275 cc., in 4 cases, with 0, 75 cc. the average output was 5,250 cc. the maximum being 6500 cc. and minimum 4,800 cc.

ERIC COELHO.

CARDIAC EDEMA : CAUSATION AND TREATMENT. C. J. GAVEY. The Practitioner 162 : 96-100, 1949.

According to Fabs (1941), if the venous pressure is increased above the normal of 5 mm. Hg. to 13 mm. Hg. or more, the osmotic pressure of plasma proteins 22mm.

Hg. is not enough to prevent fluid from leaving the capillaries and oedema forms. Raised venous pressure of 10 to as much as 50 mm. Hg. and simple venous stasis from immobility of the lower limbs results in oedema. The arms being relatively active even in very ill cardiac patients, dependent edema is not often marked in the upper extremities through venous pressure is very high. Raised venous pressure in the great veins in the neck dams back lymph from the thoracic duct, hence defective lymphatic drainage causes cardiac edema.

Abnormal capillary permeability caused by capillary malnutrition allows protein to leak out and tissue retention of fluid is promoted. Retention of metabolites raises the osmotic pressure of tissue fluid and resorption is thereby hindered. By virtue of diminished plasma protein, anæmia occasionally contributes to edema of heart failure. Another factor in the causation of cardiac edema is the disturbance of sodium ions. When these are in excess in the blood stream, the blood volume is increased and edema formation is facilitated. The reasons for the edema not becoming gross is due to the counter-pressure of the edema fluid outside the vessels. Of all these causative factors, raised venous pressure and sodium retention always dominate.

Cardiac edema is generally tender. It is detected under the soles, behind malleoli or on the shins. Pitting occurs only when the limb increases in volume by 10%.

In the treatment of cardiac edema, whatever its etiology, rest in bed is essential, and may cause diuresis and reduction of edema. The diet in acute failure may be only small bland meals but in chronic failure meat may be given which ensures in providing proteins and vitamins and thus obviates two contributory causes of edema. Schemm (1942) provided a salt poor diet, which though impracticable at home due to rationing of food, however has a definite place in the therapeutics of the irreducible forms of cardiac edema. In many edematous cardiacs, limitations of fluids to 30 ozs. a day and no added salt are sufficient restrictions if the help of digitalis and mercureal diuretics is enlisted.

In the production of diuresis, digitalization and mercurial diuretics are helpful. One helps by acting peripherally, the other centrally. Digitalization is indicated in all types of congestive heart failure except in pneumonias, in very recent coronary thromboss and in high output heart failure. Digitalization is obtained by digoxin 0.25 mg. q.d.s. for 5 to 8 days, then 0.25 B.D. or daily. McMichæl (1948) claims that mersalyl aids in eliminating sodium from the blood stream, that it has an important action on the cardiovascular system and limits resorption from the renal tubules. Ammonium chloride gr 30 an hour or two before the injection, enhances the action of the mercurial duretics. Aminophylline .2 gm. in tablet from t.d.s. for 3 days in a week is useful in slight edema, but more protracted doses cause gastro-intestinal disturbance. 2000 mg. of Vitamin C daily by mouth for 5 to 7 days have given pronounced results. These large doses of Vitamin C are not suitable for general use, but may be tried in cases of irreducible failure. Paracentesis may cause dimness especially in chronic edematous cases since the advent of mercurial diuretics, mechanical drainage by Southey's Tubes or multiple incision is not in vogue now.

ERIC COELHO.

VITAMIN B12. Edgar Jones, Amm. Practitioner. Vol. 3 : 391-392, 1949.

Liver extract in the treatment of pernicious anæmia or other macrocytic anæmias is widely known. But whether a single factor or other factors also were concerned in the hæmatologic or neurologic aspects of P.A. has been a matter of speculation. And on the basis, that more than one factor was involved for complete treatment, crude liver extracts were used in patients who showed neurologic manifestations. In 1940, a new factor was evolved termed Vitamin M or Folic acid. In 1945, experiments were done with this factor and it was found to be effective against hæmatologic manifestations but not against neurologic manifestations which are commonly seen in P.A. Indeed there was a possibility of precipitating, or at least permitting the development of neurologic manifestations in cases of Pernicious Anæmia, as was shown, by onset of neurologic manifestations with treatment with Folic acid in contrast to untreated cases.

In 1948, a red crystalline material with hæmopoetic activity was evolved which was termed Vitamin B12. Though its chemical structure is not known, it is found to contain phosphorous, nitrogen and cobalt. As little as even 3 micro-grams was able to evoke a good hæmopœtic response with rise in red cells and hæmoglobin. It has recently been found that gastric juice promotes the absorption and utilization of B12, thus enhancing its hæmopœtic activity. Recently it has been found that Streptomyces griseus from which Streptomycin is obtained, also contains it. Spies and his associates have found that anæmia of sprue responds to Vitamin B12. Thus Vitamin B12 is of value in combined system disease, but it is too early to give a final decision on this point. Though dosage of Vitamin B12 is not calculated so far, one micro-gram is suggested as equivalent to one U.S.P. unit liver extract.

Thus while Folic acid stimulates or at least does not act on neurologic manifestations, Vitamin B12 apart from promoting hæmopœtic activity, protects the nervous system. Moreover, the presence of cobalt in Vitamin B12, which was never known to be needed before in man, is an interesting discovery.

G. P. VARMA.

SURGERY

REDUCTION OF INTUSSUSCEPTION BY BARIUM ENEMA. RAVITCH, M. M. AND Mc CUNE, R. M., Ann. Surg. 128 : 904-907, Nov., 1948.

The authors record a series of 33 patients with intussusception who were treated by reduction with a barium enema. In 24 cases there was complete reduction and cure, but in 9 cases the terminal portion had to be reduced by an open operation.

No anæsthetic is necessary. A Foley bag catheter is passed into the rectum and distended with 20 to 40 ml. of air. The buttocks are squeezed together by an assistant while the barium emulsion is run in from a height of 3 feet. Under the fluoroscopic screen the meniscus-like apex of the intussusception can be followed as it retreats along the colon. Entry of barium into the ileum proves complete reduction. If it is thought that complete reduction has not occurred or if this method of reduction fails to completely reduce the last portion, an operation should be done immediately.

E. J. BORGES.

ORAL STREPTOMYCIN IN SURGERY OF THE LARGE BOWEL. THE PRODUCTION OF. SECONDARY HYPOPROTHROMBINAEMIA. HERFORT, R. A, AND STANDARD, S. Ann. of Surg. 128 : 897-992, Nov., 1948.

A reduction of the prothrombin content of the blood may occur after the administration of sulphonamides to reduce the bacterial flora of the interstines. The authors have studied the effect of oral administration of streptomycin on the prothrombin of the blood. One gram of streptomycin was given by mouth three times a day for 14 days. There was 80% to 100% diminution of the number of bacteria in the stools, together with a definite fall in the prothrombin level of the blood. This value could be restored to normal by giving Vitamin K, suggesting that the bacteria in the intestines help in producing this Vitamin. The prothrombin returned to normal after a few days even if streptomycin was continued.

The above observations make it advisable that any operation on the bowel should not be delayed beyond 48 to 72 hours after streptomycin is started orally, and Vitamin K should be given before and after operation.

E. J. BORGES.

PEDIATRICS

RESPONSE OF INFANTS TO DIPHTHERIA IMMUNISATION. BY BO VAHLQUIST. 'Lancet' 1 : 16-18, 1949.

In many parts of the European countries it has been found that the passive immunity against diphtheria in infants has considerably decreased, and there has been a gradual change for the worse.

Only a small percentage of infants born, are immune to diphtheria and thus a larger percentage are exposed to the risk of infection as early as even 3 months. But the chances of contracting diphtheria are less because (i) infants are not so much exposed to infection and (ii) their mucosa is more resistant to infection. If, however, the infection occurs, it almost always takes a mali gnant course. Therefore it has become necessary to immunize these new-born infants to diphtheria. Active immunizsation is done after 6 months of age because below that age, the child has got passive immunity and the presence of antibodies exceeding 0.1 unit/c.c. inhibits the action of antigen, thereby making the active immunisation useless.

Immunisation is done with aluminium precipitated standard Diph.-toxoid with a potency corresponding to 45 flocculations units/cc. Active immunisation was done in infants at the age of 2.3 months even and the results have been very good—equally comparable with children aged 6-8 months, older children and adults. When the mother is immunised late in pregnancy the infant gets the passive immunity to the extent of 0.1 unit/cc. and in such new-borns when active immunisation is done, it is useless. When however passive immunity is below 0.02 units/cc. no inhibition of antigen occurs and active immunisation is successful.

Vaccination on a large scale under 6 months of age should not be done except in places where there is little or low natural immunity against Diphtheria in infants. Here vaccination should be done in the first three months and booster doses given at 1 year and on entering school. However in epidemics, the child should be passively immunised by injecting the mother during gestation and later active immunisation of the child should be done as in naturally immunised persons.

G. P. VARMA.

RELATIVE UTILIZATION OF CALCIUM FROM SOYA MILK AND COW'S MILK BY GROWING CHILDREN. BY KARNANI, DE, SUBRAHMANYAN AND CARTNER. Ind. J. Med. Res. 36 : 353-360, 1948.

Experiments show that animals utilized over 80% of calcium from soya milk or cow's milk when they were on calcium deficient diet. The utilization of calcium is much less by human beings and is almost equal with soya milk or cow's milk. Comparative systematic metabolic studies were carried out in six children aged 7 to 9 years with soya milk fortified with Di Calcium Phosphate and cow's milk separately all the children were kept on low calcium basal diet for the 15 days of experimentation and for ten days before the experiment. All the children were given a completely balanced uniform diet. The 15 days experiment period was divided into three, five day groups. In the first five day group, basal diet was given, in the second, it was supplemented with soya milk fortified with Dicalcium phosphate and in the third, basal diet was supplemented with cow's milk.

Calcium excretion in the urine and fæces was estimated in all the three periods and calcium balance determined. On basal diet which provided 224 mg. of Ca.

balance was -135 mg. to -29 mg. The Ca. excretion on this low calcium diet was 278.5 mg. The addition of about 363.5 mg. of Ca. from either soya milk or cow's milk changed the balance from -54.5 mg. to + 29 mg. Calcium utilized from soya milk was 23.1% and from cow's milk 22.8%, thus showing practically same amount of utilization. Blood calcium showed an increase of 1.2 mg.% in case of soya milk and 1.5 mg.% in case of cow's milk.

Thus when the children were fed on low calcium diet, there was a negative calcium balance. When the diet was supplemented with fortified soya or cow's milk, there was a + inc. calcium balance which position strikingly similar for both was. The average utilization of supplementary calcium was only 23% on an average.

G. P. VARMA.

A STUDY OF THE USES OF TOYS IN A HOSPITAL. Grace Langdon. Child Development, 19 :197-212, 1948.

A study covering a period of approximately four and a half months was carried on at the New York Infirmary, the purpose of the study being to discover what uses toys can serve in a hospital, and to gather information and suggestions through observations of their use which might be significant in the further design and manufacture of them. It was thought that such information would have significance for educators, parents and others interested in children as well as to doctors and nurses and for the toy manufacturers.

The initial selection of toys to be used in the study was made on the basis of what is commonly known about the interests of children of different age groups in general, and the interests of ill and convalescent children in particular. Toys calling for strenuous effort were avoided. Since space was limited large toys were avoided. Since space was limited large toys were not included. All toys used had to be durable and such as could be sterilized or otherwise kept sanitary. Further noise-making toys had to be avoided, since quiet in the ward was necessary.

The findings of the study were varied and suggestive. The observation showed, that frequently a toy proved useful in tiding over some critical moment, *e.g.* the crying which often occurred as the parent departed after admission tended to diminish when some interesting toy was offered. The same thing often happened when parents left after their regular visits. Toys were given to children to while away time when waiting for an operation, and it was found that in play with the toys some of the anxiety concerning the operation, if there were such anxiety was lessened. A toy offered coincident with the approach of the doctor for dressing helped in lessening any resistance there might have been to the necessity of the moment. Observations further showed that toys were an aid to the routine of the ward, *e.g.* sometimes, a child who instead of resting wanted to visit the child next to him at day time would be given a toy and would turn attention to it, soon getting quiet enough to drop off to sleep. Toys also helped during bath time and meal times. The record showed numberless instances when toys served to turn what might have been periods of boredom to periods of happy activity : *e.g.* a seven-month old baby with one leg in a cast was used to being played with by the nurses, and when the nurses were too busy to give her attention, she began sucking her thumb. An attractive toy suspended across the crib within the reach made her bring her thumb out of the mouth, and both hands reached for the coloured rings and balls, and for the rest of her stay served absorbing enough to keep her happily occupied.

Toys are useful in maintaining children's morale under any kind of trying or unusual or difficult condition. One such instance is a 14 year old rheumatic fever patient who had been hospitalized for a period of several months. She came to accept the orders to stay in bed as her interest grew in jig-jaw puzzles and other games and puzzles which helped to increase her concentration.

Toys also proved helpful, in reducing or preventing the problem of discipline, in other words, a good substitute for mischief. Records show instances when this offer of a toy brought an impending quarrel to an end. Children busy with a toy had something better to do than chase one another around the ward. Being busy with a toy helped to reduce the aimless yelling at each other from one bed to another; a toy telephone for example turned attention to more constrictive play.

A child's inner thoughts and feelings were then revealed in his play; records show that play with miniature-lip toys, house furnishings and dolls were significantly revealing. Sometimes a child would spend considerable time in arranging and rearranging pieces of furniture commenting as he did so. Scenes of violent family fractions were played out inrealistic detail, in other cases families went out on interesting outings. Toy telephones brought out many different kinds of conversation. Interpretations were largely speculative but often proved helpful when there was no way of knowing the background of the children observed. The usefulness of toys in meeting the special needs of cerebral palsy was frequently mentioned. The toy telephone *e.g.* encouraged conversation of a kind useful for the child with speech difficulty. Manipulative toys offered exercises for hand muscles of a sort that seemed to be needed by the child whose hands did not function normally. Toys that could be used on the table as a child stood beside it helped to keep on his feet the child whose leg muscles were unsteady.

C. SIMMONS.

NUTRITION

STUDIES ON INDIAN EDIBLE OILS. GROUND-NUT OIL. BY RAMAMURTI, K. AND BANERJEE B. N. Indian Journal of Med. Research: 36: 371-387, 1948.

The nuitritive value of a fat can be considered from several view points. To serve as food, its assimilation and utilization in the metabolism are important. The first process in digestion; while later comes absorption. Oils and fats are the carriers and solvents of vitamins and caroteues. The role of Indian edible oils in this aspect of the problem is vital for the health of the nation. In a tropical country like India, oils and fats quickly go rancid, therefore the *storage* property is very important. The development of acidity on storage of nuts has been recorded and found that it is considerably increased by 'damaged' and 'splits' nuts.

I. Studies have been made on the free-fatty acidity (F.F.A.) and keeping quality of ground-nut oil and the relation of colour. It has been found that sample of the lowest acidity is the one with the lightest colour and the sample with the highest acidity is the one with the deepest colour, though in many cases, colour and acidity do not run parallel to one another.

The acidity of fresh samples obtained directly from oil mills and the 'ghani is not so high as that of market samples, yet it is sufficiently high. Inquiry showed that no grading of the seeds or selection had been made while expressing the oil *i.e* both good and bad seeds were used. When healthy hand-picked seeds alone are chosen, the acidity of the oil is less than 1%, whereas mouldy, shrivelled and broken seeds yield an oil of acidity between 3.5 and 4.5%.

Experiments show that operations carried out during refining do not improve the keeping quality of the oil to any considerable extent. While refining may lower the acidity and make the oil more agreeable to taste and odour, its effect is but little in so far as the keeping quality of the oil is concerned. Hence ann-oxidants should be used to prevent rancidity in the finished products.

II. (A) Digestibility of high-acidity ground-nut oil as measured by its rate of hydrolysis by lipase.

Fresh ground-nut oil shows a satisfactory hydrolysis and samples upto 2% acidity show a slight and gradual fall in the rate of hydrolysis. With higher acidities the fall is very rapid ; and a highly rancid sample is hydrolysed very little. The fall in the rate of hydrolysis after cooking the oil is more marked in samples possessing more than 2% F.F.A. The hydrolytic curve with pancreatic lipase shows that an acidity above 1% is undesirable. An oil with low acidity can be got if only fresh healthy nuts are used and 'damaged,' 'splits,' 'broken' ones carefully discarded. Certain amount of damage occurs to nuts during storage and transport; before crushing these should be separated from healthy ones.

(B) Effect of high F.F.A. Ground-nut oil on Vitamins and Carotene. Both carotene and vitamin A are inactivated in the presence of high F.F.A. ground-nut oil. The inactivation of Vitamin A is greater when oil is fried than when it is raw. Refining and hydrogenation do not prevent the inactivation. The addition of an anti-oxidant like progallin A is effective in prolonging the period of inactivation of Vitamin A only so long as F.F.A. of oil is below a certain limit. As the F.F.A. of oil increases the protection afforded by anti-oxidant to Vitamin A decreases. An oil of less than 1% F.F.A. causes very little inactivation of carotene or Vitamin A.

(C) Storage of ground-nut oil using Anti-oxidants. Well-known anit-oxidants are : propyl gallate, ethyl gallate, progallin H and hydroquinone.

Progallin H is found the best for ground-nut oil. The protection afforded is 2-4 times more than the untreated oil. With increasing F.F.A. in the oil the storage property is poorer and the use of an anti-oxidant then fails to protect the oil in the same ratio. The removal of F.F.A. from a high-acidity oil does not improve the storage property and even the addition of an anti-oxidant then fails to increase its storage life.

To sum up, from the point of view of digestibility, storage property and as carrier and solvent for carotene and Vitamin A, ground-nut oil below 1% F.F.A. alone should be considered suitable for edible purposes. Removal of acidity or refining a high F.F.A. oil fails to bring it to the quality of fresh low F.F.A. oil. Any oil of over 2% acidity should be rejected for edible purposes. Progallin A increases the storage property 2-4 times.

M. A. MASTER.

BOOK REVIEW

TABLET MAKING : By Arthur Little and K. A. Mitchell. Price Sh. 15, Pp. 121 with 41 illustrations. The Northern Publishing Co- Ltd., 37, Victoria Street, Liverpool 1, England.

A number of books and monographs already exist on Tablet Making in English, German and French languages. The art and technique of Tablet Making has been rapidly changing and this small book on 'TABLET MAKING' by A. Little and K. A. Mitchell is a very useful addition to the existing books as it deals with all the latest processes of Tablet Making.

The book is nicely arranged and all the processes such as, mixing powders, drying, dry and wet granulating, and compressing of tablets are fully described. Installation of machines and their care is also dealt in a manner which would help even a beginner to understand the same. Various difficulties which are generally encountered during the process of Tablet Making are clearly explained by the authors. The chapters are systematically arranged and will prove of great help to every tablet maker. The information on excipients, tablet base, and disintegration of tablets is also very exhaustively dealt with. It will help solve many difficulties, especially those which face and sometimes puzzle the beginner.

The Chapter on Coating of Tablets unfortunately, is not in keeping with the whole book. The coating of tablets, such as Sugar Coating, Chocolate Coating, Silver Coating, Gelatin and Keratin Coating, has come into great prominence these days. This part of the book is very brief and inexhaustive. It would have been better to devote some more pages to the intricacies of the process of coating and the technical tricks which are employed should have been better explained.

The quality of tablets depends on the speed with which they disintegrate in the presence of liquids. The methods of complying with this quality and of testing the same are not described.

In spite of these omissions the book is a very useful addition and should find a place on the bookshelf of every tablet manufacturer.

K. A. HAMIED.

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MEDICO-LEGAL ASPECTS OF SEXUAL DISORDERS AND SEXUAL PERVERSIONS §

H. S. Mehta*

When I was asked to read a paper before this Medical Congress, I was not sure what subject I should select. I found however, from my records that during the last few years, I have come across several cases involving sexual disorders and perversions. As I feel that such cases are unfortunately on the increase in this post-war age, I think it might be interesting to place before you some observations in this connection.

The frequency with which the question of sexual incapacity has to be decided by the Courts of Justice prompts one to invite attention to a consideration of impotence in the male and in the female. As there is some confusion as regards the term "Sexual Incapacity", it requires to be made clear that in Forensic Medicine this term is only used to connote the persistent impracticability of copulation or physical incapability of accomplishing the sex act.

From the view point of administration of justice, impotence is a sufficient cause for nullity of marriage, whereas sterility is not. The members of either sex may be incapable of performing the act, or sterile, or both. Medical opinion may be sought about these conditions in connection with claims for nullity of marriage, divorce, contested paternity and legitimacy, in charges of rape where impotence is pleaded as a defence, and in claims for damages where the loss of sexual function is alleged as the result of an accident or assault, especially if inflicted on the head, neck, or loins.

IMPOTENCY IN THE MALE.

Cases of male impotency that have come before the Matrimonial Courts may be grouped as follows :—

(1) Cases which are characterised by failure of erection; these are cases where the sexual desire is present or urgent but the erectile power is feeble and intromission is impracticable. As no man is potent all the time and in all circumstances defective erection may be temporary, even in the virile.

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§ Paper read before the Bombay Medical Congress, 1948.

Example :—In one case a Hindu male aged 29 confessed to me that he had lost his potency which till one year before had been good, due to the frequent demands of his wife during the *preceding* 8 *months.*

There is a type of male impotence commonly come across in practice called "Bridegroom's Impotence" which can be attributed to lack of self confidence or may be caused by mating with a terrified maiden with a small hymenal orifice, the husband constantly recoiling from hurting her; thus erection is hindered and this leads to premature ejaculation.

(2) Next we come to cases which are distinguished by some disturbance of ejaculation—the usual form of which is *premature ejaculation.* Cases of premature ejaculation are common amongst highly strung or highly sensitive males and in a majority of cases they are newly married men who require to be properly guided lest this difficulty may lead to permanent sexual incapacity.

Example :—In a case referred to me by the High Court last year, a husband accused of impotency within a few months of marriage, frankly admitted to me that as a result of premature ejaculation, he was losing his erection and could not penetrate; moreover he stated that he was repelled from intercourse due to an offensive smell issuing from the wife's genitals. On examination, the wife's hymen was intact. A divorce was granted on the ground of impotence.

(3) Those who suffer from sexual perversions are often unable to copulate with a normal partner, even though they may love and respect that partner. These perversions tend to become worse and are generally incurable. It is noticed that homosexuals or those with homosexual tendencies are generally impotent with the opposite sex and those who depend upon certain perversions for the necessary stimulus are impotent without them. The disgust at, or the refusal to provide such stimuli by the wife, may be the determining cause of separation. I have come across cases where wives have asked for divorce on the ground of sodomy or other perverse acts by the husbands.

(4) Some cases of impotency are due to weakness of the sexual desire. The strength of sexuality varies in different men being dependent upon psychological make up and endocrine pattern. In some cases of weakness of desire one sees a weakly-sexed man married to a well-built passionate type of woman with whom he may attempt sexual intercourse when he has little or no desire for it; sooner or later he fails and failure undermines his confidence in his sexual capacity and eventually he becomes a case of functional impotence.

Example :—I was asked to examine a tall and hefty woman and state whether she was a virgin. The examination revealed that the genital parts were dilated as found in a woman accustomed to sexual intercourse. She gave the history that her husband was a thin lean man who very rarely showed the desire for sexual intercourse and if he attempted he failed due to lack of erection. Later on in order to stimulate his wife he used to do fingering. It is likely that repeated fingering had brought about dilatation of the part so that I could not be sure whether dilatation of genitals was due to fingering or intercourse.

IMPOTENCY IN FEMALES.

The frequency with which nullity suits are filed by women has given rise to an impression amongst lay persons that impotence is peculiar to the male, but in reality it is not so. Women are also impotent either from developmental anomaly or mainly from psychogenic causes.

There is an inherent difficulty in establishing sexual incapacity in women due to developmental defects, because so long as penetration even partial into her vagina is possible, it is sufficient to prove her capacity in law; and as her passivity is disregarded, the effect of general disease and disability does not exert the same influence as it does in the male who is the active agent. In other words existence of a normal vagina renders copulation possible at any time even if there be no response.

Cases of psychic impotency in females are also common due to sensations and emotions playing a chief part and such cases are frequently met with in practice in highly strung and hyper-sensitive women.

In other cases psychic impotency in women is due to inhibitions developed, on account of defective virility of the husband, or a psychic tie with another man, or an instinctive aversion to her own husband.

VAGINISMUS.

One local condition in females deserves special mention as regards impotency, viz., vaginismus. At times the husband sues the wife for divorce on account of her impotency due to "vaginismus" which is a spasm of the vagina or rather of constrictor vaginae with severe pains, which occurs at the time of the sex act and prevents the entry of the penis into the vagina. One comes across milder cases of vaginismus as a result of ulcerations, fissures, or other proveable conditions like tough inelastic hymen, which are easily amenable to treatment but there are some cases of vaginismus where no local lesions are found and they alone are of medico-legal interest. In such cases of vaginismus, the spasm of vagina is of such a nature as to make penetration impossible.

Vaginismus causing complete failure of intromission of the penis is of very rare occurrence and in such cases when a genital examination is undertaken of the hymen and vulval outlet, by attempting to pass a glass rod through the hymenal orifice, the glass rod is firmly grasped due to contraction of the sphincter of the vagina; as an alternative, if the inner aspect of the vulva is touched with a small camel hair brush, such agony is caused that the patient shrieks and complains of pain as if someone were cutting the part.

I have come across very few cases of the above mentioned type of vaginismus eliciting a positive test.

Example :—I remember a girl of 18 years who had left the protection of the husband on account of his sexual perversion. The girl was found to be accustomed to sodomy but was a virgin. The husband frankly admitted that he could not effect penetration into the vagina as the girl screamed at the time of the sex act; so he later on resorted to unnatural intercourse by force.

Example :—To quote a reverse example a case came before the Divorce Court early this year wherein the wife charged the husband with impotency which was denied by the husband who inter alia laid a counter charge against the wife of not allowing penetration due to vaginismus. The wife was examined by me and found by me from the above mentioned tests described that she was a virgin and *apta vira*. The husband was examined by two other learned colleagues of mine who testified as regards the physical components of potency of the husband but naturally were not in a position to opine about the psychic component. The wife got a divorce and the husband was considered impotent as far as she was concerned, in other words "relatively impotent".

Impotence in males as well as females may be temporary or permanent, remediable or irremediable, and may be absolute, signifying failure in all circumstances, or relative, signifying failure in certain circumstances although potent in others.

Example :—My series notes a case of an officer who was happily married for seven years though sterile; then some disagreement arose between the two and both were estranged. The wife sued the husband for divorce on the ground of impotency. She produced a medical certificate of being a virgin; the husband for reasons best known to him did not defend the suit and the case was decided *ex parte* in favour of the wife. The wife remarried within a couple of months after divorce and the husband followed suit a few months later. Now both the original parties have each a child, after their second venture. Without casting any reflections on the parties of having obtained the divorce by collusion, as happens sometimes and relying on the medical certificate of the wife, one may say that it was a case of Relative Impotency.

When a case of impotency comes before the courts, both the parties are subjected to an examination, not by the same panel of doctors as, in my opinion, should be done, but each is examined by a separate medical person due to an aversion on the part of the woman to undergo examination by any other than a lady doctor. This leads to an incongruity in the report presented, if the lady doctor states about the wife being *virgo intacta* and *apta vira* while the medical man who examines the husband states that there is nothing to suggest that he is not capable of sexual intercourse, that is, he is potent; because in absence of injury, disease or defective development of the genital organs, an otherwise healthy man must be assumed to be sexually capable.

Whenever such a person is referred to me, it is requested that the wife may be also examined in order to arrive at a definite conclusion whether the husband is sexually incapable, provided that the wife was a virgin at the time of marriage.

From the certificates presented to the courts, I have often noticed that the medical opinion is too dogmatically stated that the husband is potent or impotent, without the examination of the wife. If the doctor is satisfied regarding the potency of the man who has been examined alone, it is wiser to state that the genital organs are of normal development, that there is no disease of inflamatory nature in testis or epidydimis, and evidence of organic disease of nervous system and there are well marked secondary sex characters. From all these it can be concluded that he has no impediment, congenital or acquired so as to preclude him from the performance of the sex act. Thereby the opinion is safeguarded against a possibility of the cases being one of psychogenic impotence as majority of cases of impotency are and for which no opinion could be given.

At times the court inquires whether the impotency is remediable or not. As the treatment of sex disorders is not the object of this talk, it may be just mentioned that upto now dismal failure is obtained with treatment by organotherapy and the unfortunate persons inflicted with the disability ultimately fall prey to quacks.

Psycho-therapy in the form of narco-analysis has opened a new vista and gives some hope of cure in these cases. Here, while the patient is under the influence of sodium amytal or penthothal, his sub-conscious self is revealed to the doctor who may be able to get a valuable clue as to the cause of the sex disorder. Unfortunately the medical man cannot directly question the person later regarding the matters which the patient spoke subconsciously during narcosis, because a reverse effect is produced and the patient refuses to receive further suggestions under narcosis for cure of impotency.

My statistics of such cases are not large enough for me to pronounce any definite opinion but from my experience of this mode of treatment I know that a few cases of psychogenic impotence have regained their potency under this type of suggestion therapy.

SEXUAL PERVERSION.

Now we take up the deviation of the sexual impulse viz. sexual perversions.

Nearly every person has a deviation from the normal in his sexual life, which however slight shows leaning towards perversion and perversity. For this reason an opinion of abnormal sexuality must be pronounced cautiously.

From the medico-legal point of view sex perversion i.e. a disease, requires to be differentiated from perversity i.e., a vice.

Sexual perversion is taken to mean a congenital condition or one that has existed for a long time whereas perversity means an acquired vice. Sexual perversion is psycho-pathological whereas sexual perversity is vicious. A true sexual pervert is not master of his will, so that when perverted sexual practices are employed e.g., in sadism etc. it is necessary from the medico-legal point of view to differentiate between a person who acted through an irresistible impulse denoting an insane mind and the one who acted through an impulse which could easily be resisted, showing a depraved mind for which he ought to be punished.

TYPES OF SEXUAL PERVERSION.

Perhaps the most striking of these are cases of Homosexuality also called Sexual Inversion or Unisexual Love. Here, a morbid attractions for the same sex is met with in varying degrees from mild prediliction for the same sex, associated with normal inclinations, tó complete inversion with the horror of the opposite sex in sexual relations. The sexuality of the affected individual is also subject to inversion, and though abhorent fo woman, may retain the active role or may play the passive part in the sex act. Many homosexuals satisfy their sex urge by kissing, embracing or even touching the opposite person while others do so by mutual masturbation. The very personality of a homosexual man or woman may differ from that of a normal heterosexual individual. I have observed that the skin of a homosexual is warmer than that of a normal man or a woman and is soft. Their outlook is coloured and they look upon themselves as martyrs and consider themselves victims of fate and that they can no more alter their sexual reactions than the heterosexual can alter theirs. These are individuals who are often conscious of their acts and of the social faults that they commit; but as they are usually the victims of an uncontrollable impulse, they are not truly responsible for their acts.

They require medical treatment rather than imprisonment and every effort should be made to help them to get rid of this perversion.

Example:—I have come across a number of such people who were repeatedly brought to me for examination for their overt homosexual practice and were sentenced more than once to imprisonment. They have often begged of me to cure them of their perversion weakness and in return offered their services to the institution free. A medical jurist feels concerned when such a person is sent to jail, because he may be guilty in the eye of the law, but perhaps no more guilty than an insane person.

In this category I certainly do not include those pests of society who should be held responsible for the depraved acts that they perform having full consciousness of it through perversity; nothing forces them to this diabolical practice except immoral considerations which they could perfectly well resist. The inversion of genital instinct is entirely artificial in them and Society requires to be protected against them.

ALGOLAGNY.

There are two classes of sexual perversions where sexual excitement and pleasure are obtained by inflicting pain on the object of lust or by suffering pain at the hands of that object. The term algolagny is used to designate these two classes of perversions. The active form of algolagny where sexual excitement is experienced through causing pain to others is termed "Sadism" while the passive form where sexual satisfaction is experienced through suffering pain or humiliation from the chosen consort is termed "Masochism", which is the exaggerated female trait of submission to the conquering male. It must be noted that there are many males who are masochists and many females who are sadists. "Sadism leads to most violent outrages against living things and Masochism to most fantastic humiliations of human nature."

Sadism.

The Sadist, impotent for normal sex, may derive his sexual excitement and gratification from acts of cruelty which he inflicts on his victim, accomplishing his orgasm without even attempting coitus, or, impotent without the acts of cruelty may succeed in getting erection through excitement which the maltreatment of the object of his lust gives him and thus he may be able to effect penetration and finish the act with normal sexual intercourse.

Example:—I have come across a case of a woman masochist who developed melancholia and a strong aversion to the husband; while going over her sexual history she stated that she developed a dislike for the husband as she felt that his love was waning because he was not handling her roughly enough during the sexual communion and hence she was not deriving the pleasure which she used to get before.

A girl of 14, who had left her husband's house, was brought to me by the Police. She stated that her husband treated her cruelly during the so-called sex act. He used to walk on her body and ejaculated outside when she screamed and groaned with pain. The husband looked mentally abnormal and admitted the facts narrated by the girl. She was found to be a virgin.

Sadistic Murders.

The Sadist of the most extreme type is the sadistic murderer. For him killing of his victim is the *sine qua non* of sexual, gratification.

Example:—In my series there is a case of a potent sadist, a hotel keeper, who commenced normally performing the sex act with his young mistress and strangled the girl during the acme of excitement.

After having committed the murder, he went to the Lamington Road Police Station and surrendered himself. He admitted to me that the victim was his mistress for several years ; and that lately he felt that his erectile power was waning. He added that he felt much excitement when he touched her neck and that subsequently he developed a vicious desire to strangle her which many times he overcame. On the day of the incident, he could not check the impulse and at the height of excitement he strangled her. At the postmortem examination of the girl, I found spermatozoa in the vagina of the victim and marks of strangulation on the neck.

The law awarded him the maximum penalty though I believed him to be a sexual pervert.

Sadistic acts with animals and birds are fairly common.

Example :—My series notes a case of a boy, aged ten, of precocious development, who used to go after hens and with delight used to twist and break their necks. On being admonished by his parents, he begged to be forgiven promising not to do so again, but his resolution would vanish on seeing hens again. Once he was observed suspiciously moving round the cradle of his infant sister and was in great ecstasy. His parents got alarmed and brought him to me. I found him mentally abnormal and certified him a lunatic.

Exhibitionism.

Another type of sexual perversion is Exhibitionism in which there is uncontrollable desire to expose the body and generally the sexual organs to the gaze of others. In pathological exhibitionism which brings a sexual pervert within the pale of the law, the urge to exhibit himself is impulsive, rises suddenly and is irresistible. In contrast to this exhibitionism, there is the exhibitionism done by wicked persons who prowl around public schools and play grounds and exhibit their genitals with the nefarious motive of enticing young persons of immature age.

Example :—In my series I have come across an old man of 70 who was a pervert exhibitionist of his *mohla* and was about to be manhandled for his perversion when the Police rescued him and brought him to me. He told me that he was unable to control his exhibitionist tendency on seeing young girls and was not desirous of the sex act at all. His examination revealed that he was a partially demented person not responsible for his acts.

SEX CRAZY WOMEN (NYMPHOMANIACS) AND LUST MAD MEN (SATYRS)

Satyriasis and Nymphomania mean abnormal sexuality in male and female respectively. Those cases of satyriasis and nymphomania due to cerebral causes, are the only ones of medico-legal importance, as they may lead to public offences against decency or by their excessiveness the health of the husband or wife may be endangered.

My series mainly notes cases of Satyriasis.

Several young girls of 14 to 16 are brought to me by the Police, who have left their husbands, because they are unable to meet their sexual demands and have ultimately learnt to regard the sex act as loathsome. When the husbands of such girls were produced before me, I noticed that most of them were huge well-built men, about 15 to 29 years older than their respective wives who were usually frail and weak. On being reproached for tormenting their wives, they asserted their inherent right to have sexual congress as many times as they liked, within 24 hours.

A case of Nymphomania.

Example :—A decent educated lady of good family was drifting to psychoses and her sex urge had gradually inreased to such an extent that she used to insist on her husband to have intercourse several times in 24 hours. When the husband could not meet the advances and felt exhausted, she used to become violent and show a sadistic tendency by biting the husband.

During my interview she used filthy language, unbecoming of a lady and cursed her husband for lack of vigour. Ultimately I had to certify her as a lunatic. Those satyrs and nymphomaniacs who eventually get demented and come within the pale of the law are brought to me for mental examination and certification. I find they remained naked most of the time making indecent gestures and indulged in imaginary sex acts. Some of these unfortunate satyrs even tried to thrust the penis in the latch of the cell doors and received injuries.

PYGMALIONISM OR LOVE WITH STATUES.

This is a queer form of sexual perversion in which erotic excitement is caused by gazing at or touching statues, or undraped figures. The excitement is so great that it serves the purpose of normal intercourse.

My series notes a case of a young student of Arts who started first showing reverence for a marble statue he had; later on he was observed masturbating before the statue, and ultimately got demented.

Thus we have considered the curious abnormality of the sexual urge. It is indeed a tragic fact that sexual deviations frequently appear now-a-days as pressing problems requiring immediate attention of the medical and psychiatric professions. The reason why many human beings have succumbed to unnatural sexual desires is the stress, strain and excitement of modern civilisation coupled with a low economic standard and an innate desire for variable sensation.

On personal enquiry from those who have studied the conduct and habits of animals, it is learnt that as yet not a single case is noted even of the most ferocious beasts being addicted to any perverse practices.

It, therefore, seems that the sex perversions are found only among men and women, nature's grandest creations. Truly it can be said, "*All beasts are imperfect animals, Man alone is the perfect brute.*"

As every human being to a certain extent shows some abnormality in the performance of the sex act, there is a very thin dividing line between what is considered a righteous from a wrong act, between normal and abnormal working of the mind. Because of this, it becomes difficult sometimes to distinguish a case of Sex Perversion from one of Perversity.

LEGAL ASPECT OF PATHOLOGICAL SEXUALITY.

According to the legal codes of all civilised countries those who commit perverse sex acts are punished because it is one of the primary duties of a State to protect chastity and to maintain at least a fair standard of sexual morality.

The clinical records of this city for the past several years show that sexual offences are on the increase as far as offences against children under the age of 14 are concerned. The layman usually attributes this increase in crimes to the fact that the general morality of the present generation is declining steadily and that the offenders are not punished as deterrently as they used to be, say thirty years ago. On the other hand, the social medical worker who is apt to view the matter from a different angle, rightly considers that the increase in moral offences is due to the defect in the upbringing of children in our days inasmuch as there is considerable scope for all kinds of sexual excitement which leads to sexual excess, and exhausts the sexual capacity of a person, ultimately compelling him to indulge in perverse sex acts.

In Sexual Perversions psychopathic and neuropathic conditions play a great part; consequently before punishment is inflicted in such cases, the judge or magistrate should ascertain whether the alleged offender can really be held responsible for his abnormal sex act.

Psychiatry and Psychology which till the last war were considered blind alleys, can justly be acclaimed as the pioneers which have brought to light the psychopathological aspects of various abnormal sex acts for which a person should not legally be held responsible.

It is indeed a tragic fact that as far as mental diseases and sex crimes are concerned, law and medicine do not see eye to eye. Those whom law considers guilty may not be so in the eyes of the medical man and it is unfortunate that a person afflicted with sexual perversion is sentenced to jail instead of receiving treatment in a psychiatric clinic.

In order to decide whether a sex crime is committed either as a result of a diseased condition of the mind of the perpetrator, or due to an immoral act of the person, a thorough medico-legal inquiry is undertaken, when the present and past history of the person is examined in detail from an anthropological and also a clinical point of view. The final decision as regards the culpability of the perpetrator depends on whether there exists any abnormal mental trait in him, which might absolve him from the guilt. This is absolutely necessary in order to differentiate a diseased mental conditon of the person from immorality for which he may justly be held responsible.

As regards sexual offences, it may be argued that it is doubtful whether the existing punishments are most suitable for the purpose for which they are designed ; more good could be done by psychological and medical treatment than by incarceration in a jail.

Let all the specialists of Medical Science join hands—Physicians, Surgeons and Obstetricians—to bring about that mental attitude when sex shall be looked upon with the respect that it deserves, and women will get the reverence due to them, and then there shall be no more sexually abberated and mentally perverted people so that there shall arise no question of medico-legal aspects of sex.

May that Utopean year be soon inaugurated so that the medical jurist, forlorn as he already is, shall go permanently into oblivion. Till then eternal vigilance over human behaviour—particularly during adolescence shall be the watchword, as valid in Arts as in Science, in Sex as well as in Politics.

SOME OBSERVATIONS ON RADIOLOGICAL DIAGNOSIS OF DISEASES OF THE GALL-BLADDER§

R. F. Sethna*

In the X-Ray examination of the gall-bladder, the best technique and attention to minute details in preparation of the patient are absolutely essential if we are to reduce errors in diagnosis to a minimum.

To a physician or surgeon, a correct diagnosis in diseases of the abdomen is not always possible without the help of a radiologist. The radiologist offers his co-operation fully alive to his responsibility, as he realises that the ultimate treatment will depend upon his diagnosis.

PROCEDURE.

As a first step, a plain radiogram of the abdomen is taken after correct preparation of the patient. This may show any radio-opaque gall-stone, a renal calculus or any extraneous shadows of no clinical significance.

GALL-STONES.

They may be single or multiple, and may vary in size from a grain of sand to a large one that may completely fill the gall-bladder. The density of their shadows will depend upon the percentage of calcium content. The calculi may be rounded, faceted or irregular in shape and outline and cast a shadow of homogeneous or mottled density. When the gall-bladder is packed with calculi, it has a mosaic appearance.

Varieties of Gall-bladder Calculi :—

1. Pure Cholesterin :—these are transparent calculi and hence are not visualised in a plain radiogram. They appear as negative shadows in dye-filled gall-bladder.
2. Cholesterol-Calcium :—they cast faint shadows as they contain very small amounts of calcium and a large percentage of cholesterol (75 to 90%). They appear as white ring shadows.
3. Cholesterol-Bilirubin-Calcium :—Commonest variety. These are as a rule polygonal or faceted in outline and when multiple, produce a mosaic appearance.
4. Bilirubin-Calcium :—Usually small in size.
5. Calcium carbonate calculi and cholesterol calculi formed round a nucleus of bilirubin-calcium are rare.

Even after the finding of a gall-stone on a plain radiogram, cholecystic examination is indicated for the exact location of stone or stones and to uncover unsuspected disease in the biliary tract. No opinion should be expressed as to the exact number of calculi as some undetected ones may be obscured by shadows of other calculi or their density may be insufficient to cast a shadow on a radiogram.

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TECHNIQUE OF CHOLECYSTOGRAPHY.

The intensive or double-dose method is very largely employed for visualisation of the gall-bladder. There may be, however, some minor modifications according to the likes and dislikes of the radiologist. Detailed instructions are given to the patient as to diet and mode of ingestion of dye and it is made certain that the patient has followed them correctly to avoid errors in diagnosis. The Germans who have always been pioneers in every advance in this branch of medical science, first introduced Biliselectan for oral cholecystography in 1940. In about 1944, the British and the Americans followed suit, and this preparation is employed universally under different names, like Pheniodol y-phenyl-(B-4-hydroxy-3 : 5-di-iodophenyl) propionic acid and Priodax. The usual dose is 3 gm. This contrast medium cannot be used for intravenous cholecystography as it is insoluble.

This new product has great advantages over the old contrast medium tetra-iodo-phenolphthalein in that it casts a much denser shadow. Diarrhoea and vomiting are practically absent and hardly any dye remains in the bowel to obscure the gall-bladder shadow. Radiograms are taken at 14 and 16 hours after dye ingestion. It is necessary to take radiograms in the prone and erect postures and if required in the oblique position also. Erect posture radiograms are important because pure cholesterin calculi are obscured by the dye-filled gall-bladder shadow in the prone posture. In the erect posture the calculi either sink to the lower pole, or float horizontally in the dye-filled gall-bladder, producing translucent shadows. This position is also useful in suspected pericholecystic adhesions and in differential diagnosis of calculi and tumour, the position of the latter remaining fixed in different postures. If a gall-bladder shadow of normal uniform dye concentration is obtained a "motor-meal" consisting of the yolk of two eggs and bread and butter is given and radio-grams are taken at 15 and 30 minute intervals, and later at one hour intervals till the gall-bladder is empty of dye. Normally the gall-bladder is reduced to about half its size at the 30 min. examination and is empty in about 1½ to 2 hours. Sometimes calculi which were not revealed earlier will be visualised in the contracted gall-bladder shadow. A delayed rate of dye excretion is indicated if the gall-bladder retains fair amount of dye upto the three hours examination.

NON-VISUALISATION OF GALL-BLADDER SHADOW.

Before describing the pathological conditions responsible for non-visualisation of the gall-bladder, it would be well to consider certain fallacies inherent in the test. Three factors, other than pathological conditions, may result in non-visualisation: 1) Errors on the part of the patient. 2) Faulty technique. 3) Physiological stasis.

1. *Errors on the part of the patient:* Hysterical patients will tell lies as to ingestion of dye. Vomiting, diarrhoea and faulty diet are also responsible for wrong results. In hospitals, nurses and very busy housemen may forget to give the dye to the patient or give it at the wrong time.

2. *Faulty technique:* Faulty technique, bad radiograms and an impure contrast medium are other sources of error under this heading.

3. *Physiological stasis:* This is considered an important cause of non-visualisation of the normal gall-bladder shadow. The diet prior to examination does influence the result. In patients who have been on a fat-free or low fat diet for a long period, the gall-bladder is unable to concentrate the dye as it is already distended with thick bile contents. Correcting the diet or repeating the test will eliminate this source of error.

If all the above sources of error are eliminated, it may be confidently asserted that non-visualisation indicates gross pathological lesion of the gall-bladder which usually requires surgical intervention.

PATHOLOGIC CAUSES. The commonest cause of non-visualisation is chronic cholecystitis with or without gall-stones. Other causes are a calculus in the cystic duct, or inflammatory or malignant lesion of the duct.

Extra-biliary causes of non-visualisation are rare (less than 5%). They are extensive liver disease, pancreatic tumour, tuberculous peritonitis with adhesions, peptic ulcer or rarely a reflex condition due to ileocæcal pathology or renal tumour. In all cases of non-visualisation a second examination is always done; not to do so would be serious negligence on the part of the radiologist, because it might entail an unnecessary suffering to the patient if a laparotomy is performed. In making a diagnosis of non-visualisation one must be sure that the gall-bladder has not been previously removed.

POOR VISUALISATION OF GALL-BLADDER SHADOW.

Poorly functioning gall-bladder with or without stones is an important cause. In this group in the majority of cases the gall-bladder throws a shadow of faint intensity due to poor dye concentration by a diseased mucosa of the gall-bladder. If pure cholesterin calculi are present, they appear on the radiogram as negative or translucent shadows in a dye-filled gall-bladder. In this country, I think, pure cholesterin calculi are a rarity: I have seen only three cases upto now. This, I believe, is because patients do not seek medical advice till the abdominal pain is persistently severe enough to force them to do so. Radiograms should, as I said before, be taken in different positions, the erect posture being the most important. It will invariably happen that the calculi at operation will be greater in number than that seen on a radiogram.

CHRONIC CHOLECYSTITIS.

The radiologist finds himself in difficulties in the diagnosis of mild chronic cholecystitis. It is commonly called lipoid cholecystitis, cholesterosis or strawberry gall-bladder. We depend upon two main features for the diagnosis of this condition—: the intensity of the gall-bladder shadow and the rate of emptying of the gall-bladder.

It is difficult to differentiate between a faint shadow and a normal shadow. This is learned by experience and not by any shadow index. One can be much more definite in recognising the shadow that is faint with present day technique using the new opaque medium. Secondly, if the gall-bladder retains a fair amount of dye upto 3 hours after a motor-meal, one is reasonably certain of a diagnosis of pathological gall-bladder. In such cases, radiological examination of the gastrointestinal tract for some associated findings such as compression, deviation of position or functional derangement of these organs will help us to come to some definite diagnosis.

BILIARY DYSKINESIA.

This has aroused considerable interest amongst clinicians and. radiologists. Biliary Dyskinesia is a functional neuro-muscular derangement of the gall-bladder. The diagnosis is made on clinical and radiological findings. Two types are distinguished; the first, hypertonic caused by overaction of the vagus, and the second, atonic due to stimulation of the sympathetic.

The hypertonic type occurs in the younger age group around 30 years, the atonic in older subjects, the majority of them being women. The symptoms in both types of cases are the same ; viz. gall-bladder pain.

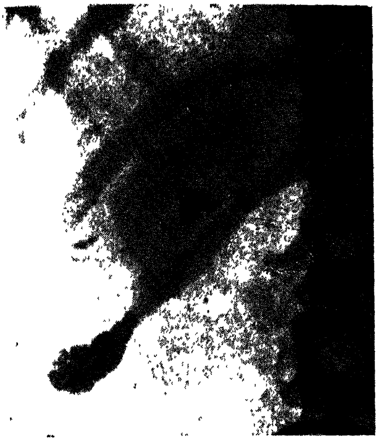
Radiograms in the hypertonic type show a spherical gall-bladder shadow which does not change its shape in different positions.

The atonic variety shows a long thin gall-bladder shadow which changes its shape with variation in posture. Both types show delayed emptying after a fatty meal. Ducts, especially the common bile duct, are easily visualised and this is considered by some as a sure sign of biliary dyskinesia. Visualisation of the duct is due to spasm of sphincter of Oddi.

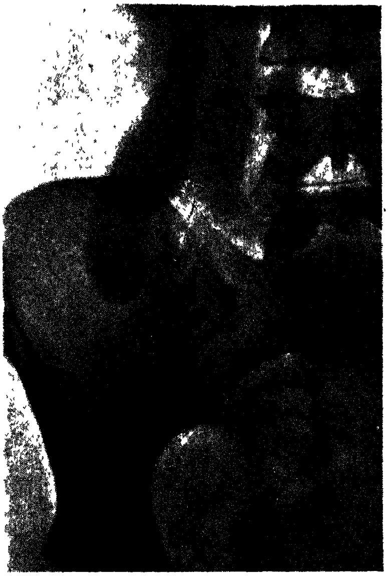
CONTRA-INDICATIONS FOR ORAL CHOLECYSTOGRAPHY.

There are very few contra-indications for oral cholecystography. Acute abdominal conditions and acute coronary disease are the most important. In cases of peptic ulcer, dyskinetic condition of the gall-bladder is often encountered. Jaundice is no contra-indication, as the contrast medium does not harm the patient ; on the contrary, cholecystography gives us valuable aid in differential diagnosis. If in presence of jaundice gall-bladder fills and empties normally, liver disease (hepatitis) is the probable cause ; if however a gall-bladder shadow of good intensity fails to empty (reduce in size) after a fatty meal an obstructive lesion is to be suspected.

Radiology has now become an exact science. This is borne out by correct results of cholecystographic examinations confirmed by operative findings in 90% of all cases of gross pathology as well as mild cholecystitis. This has happened in other countries and I feel sure that with proper and exact technique we, in this country, can obtain the same high percentage of correct diagnosis. I would appeal for the closest co-operation and team work between the physician, surgeon and the radiologist.



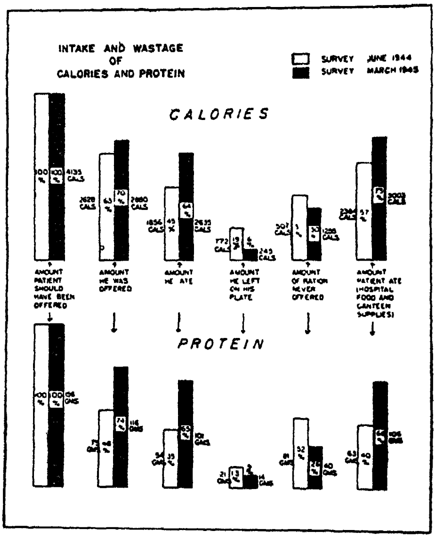
Multiple faceted calculi (cholesterol-bilirubin-calcium) producing mosaic appearance and calculi in cystic duct.



Dilated atonic gall-bladder with calcified glands.

Small calculi (multiple) mainly calcium carbonate.

Large oval single gall-stone.



Graph showing the daily intake and wastage of calories and protein of patients in a Canadian military hospital before (white) and after (black) an educational campaign planned to improve hospital nutrition.

POST-OPERATIVE METABOLIC DISTURBANCES AND THEIR CORRECTION BY NUTRITIONAL MEASURES

R. G. Chitre*

Peters[45] points out that inspite of the discovery of new agents and techniques which have reduced mortality and complications and permanent disabilities, the over-all duration of the period the patient spends in the hosptital and disability has not been reduced. He states that loss of strength and undernutrition were prominent among the factors which appeared to retard convalescence and rehabilitation. This could probably be due to inadequate feeding in hospitals. Stevenson and others[48] have reviewed the various factors which are probably responsible for the existing unsatisfactory condition of hospital diets. In Royal Canadian Army Medical Corps Hospitals, in Canada, where the observations were made, the losses of weight in patients admitted were enormous, ranging from 10 to 60 lbs. This was primarily due to 'toxic destruction' of proteins ([4], [52]). The ration scale of R. C. A.M.C. hospitals in Canada from which ordinary or full diets were prepared was liberal. It constituted 150 gms. of proteins, 144 gms. of fat and 539 gms. of carbohydrates, giving about 4100 calories. According to these authors, this liberal quota was not properly ingested, the reasons being (a) the hospital did not indent properly, (b) wastage in preparations, (c) wastage on plates and (d) number of other contributing factors, such as lack of proper supervision by medical and nursing staff, ignorance of the patient and miserly outlook of the administrative staff leading to inadequate supply of food materials and cooking equipment.

The contributing factors existing in Canadian hospitals are also existing in many hospitals elsewhere where poor patients are admitted and medical aid is looked upon as a charity. However, the existing disappointing conditions could be controlled to a certain extent by a proper educational campaign planned to improve hospital nutrition. This result was achieved when such a campaign was carried out in some of the Canadian military hospitals as shown in figure I.

Along with the educative campaign the dissemination of the knowledge of the nutritional requirements during convalescence among the hospital staff would surely yield beneficial results. From this point of view the problem of nutrition in surgery has been investigated from time to time [16, 21, 22, 23, 25, 32, 33, 34, 36, 58]. A large amount of literature has accumulated in scientific journals on this subject both in western countries as well as in the United States of America. A complete review is therefore almost impossible within a short space. Attempt is therefore made to review only those records which would help to understand the salient points of the subject.

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For proper assessment of nutritional requirements during convalescence it is first necessary that one should understand the various metabolic disturbances likely to occur during surgical procedures and after burns. It is therefore intended to treat the subject matter in two parts. Part (I) will deal with the metabolic disturbances during surgical procedures and Part (II) will deal with the methods of correction by proper nutritional measures. (Part II will appear in a subsequent number.)

Part 1

METABOLIC DISTURBANCES DURING SURGICAL PROCEDURES AND AFTER BURNS.

During convalescence after injury or burns the nutritional requirements are often great primarily because of the 'toxic breakdown' of tissue protein. Such destruction is responsible for numerous metabolic disturbances in the body. Elman[20] defines such conditions as ***acute starvation.*** According to him the causes of such starvation are those which lead to deprivation of one or more nutritional requirements. There is another factor which increases the need for one of them. Another cause is abnormal loss of protein in exudates of one type or another from damaged tissue or from large open wounds. In addition to these, sometimes an infection of one type or other may complicate the matter leading to anorexia and anemia.[35] Cuthbertson[8] has pointed out that the physiological response to trauma, in particular its metabolic component, exibits a very complex problem. After injury there is an immediate and well marked disturbance of cellular vitality in the damaged zone. The capillaries dilate and their permeability increases leading to 'reactionary oedema' depressing local metabolism. The effect of the lesion spreads and there is a discharge of leucocytes from the bone marrow. The interrelationship between such manifestations and the liberation of nucleic acid, its derivatives, and other metabolites in the circulating system is not certain. Some of the manifestations might also be due to vasomotor reaction. The vaso-constriction which results especially in the young, is a compensatory effort to offset the decreased blood volume and protect vital centres against harmful effects of low pressure[24]. Menkin[42], [43] has identified a crystalline nitrogenous material which increases capillary permeability and the migration of leucocytes. The vaso-constrictive adrenaline mechanism has been shown to play the part of a compensatory mechanism provided the damage done was not immediately fatal.[44] The local developments on the other hand may be such as to cause the general situation to deteriorate and lead to development of manifest shock. The compensatory mechanism exhibits a definite depression. This stage is followed by increase in local metabolism (traumatic inflammation) characterised by increased cellular activity of the repair process, by the lysis and effluxion of the damaged tissue elements, and what appears to be an increased and apparently generalised katabolism, especially of proteins.

Reduced oxygen consumption has been shown to occur by Davis, [18] by Aub[1], [2] and Gesell and others[26]. These changes are accompanied by certain profound alterations in the biochemistry of the blood which varies according to the stage of depressed vitality or compensatory reaction. There is clear evidence of profound cellular disturbance. It is characterised by increase in potassium content of blood and tissue fluids.[51] Increase in creatine has also been noted[3]. Other changes are hyperglycemia[6] and nitrogen retention in the blood [52], [53], [54].

Local physico-chemical studies have shown that tissues of cleft-like gaping wounds contain more than normal amounts of fluid. This increase occurs rapidly reaching its maximum at the end of the first day. Gradual decline follows till normal is reached in the third week. The *increase in water content* brings an influx of electrolytes. Concentration studies have shown that there is increase in calcium and potassium and a corresponding decrease in sodium chloride in serum.

As a result of stasis in the vessels there is accumulation of CO_2 and the products of cellular damage. There is a fall of body temperature exerting restrictive influences on the effect of asphyxia. This stage is beneficial provided it is followed by enhanced cellular activity. In shock, body temperature is generally lowered despite diminished peripheral circulation. The reduced total metabolism and volume of circulating bodies are dominant features. Of all such changes the tissue asphyxia is probably most dangerous. It may be that the hyperglycemia associated with asphyxia and hemorrhage is an attempt to maintain the nourishment of the cells in the face of failing blood supply. *In vitro* experiments have demonstrated that the increase in permeability of erythrocytes which occurs during storage of blood and which leads to increase in plasma potassium is restricted by the addition of glucose to the blood.[29]

After the period of lowered metabolic activity or 'ebb' the metabolic activity increases with the onset of traumatic inflammation. This process precedes actual repair and is characterised by hyperæmia, exudation and leucocytic emigration. Cuthbertson[8],[12] terms it the *'flow period'*. The diminished and altered metabolism attendant on this tissue injury plays a part in stimulating the repair process. Carrel[13] and Baker [14] have shown that higher cleavage products of certain proteins act in stimulating cell proliferation.

Careful studies were undertaken regarding the metabolic disturbances in such cases. It was found that after the injury there might be *relative or absolute anuria* occasionally lasting for 24 hours, while in other cases there was little apparent disturbance of urine formation. After a period of depressed metabolism the output rose slowly and often irregularly. The maximum volume was usually not attained until about two days after the maximum excretion of nitrogen had appeared. The earliest specimen of the urine available indicated the presence of relatively normal amounts of nitrogen, sulphur and phosphorus but these values rose rapidly. In the case of nitrogen the value sometimes rose to two or three times the intake. The maximum was as high as 23 gms. a day. This was reached on an average, between the 4th and 8th day of injury. In the group of post operative cases this value was reached rather earlier, usually on 2nd to 4th day. The output of sulphur coincided with that of nitrogen. The study of the sulphur nitrogen ratio of the total excess output indicated that the substance being katabolised was apparently in the main muscles and this was also supported by phosphorus to nitrogen ratio. The maximum total loss during ten days might even reach as high as 137 gms. of nitrogen with a resulting reduction of the nitrogen content of the body amounting to 7.7 per cent.

Attempts were made to establish correlation between the loss of nitrogen and the tissue damage without success. It was noted that injury such as dislocation of an ankle with slight tissue damage might produce as great a disturbance of metabolism as splintering of bones of the legs. An operation of venesection without 'blood letting' was sufficient to cause increase in output of nitrogen and sulphur. Waugh[75] has shown that there was excess of urea excretion[12], [28], [30] in case of bone and joint suppuration.

There was a regular rise in the body temperature. The general trend of the curve was paralled to that of urinary nitrogen but preceded it. The rise seldom exceeded 3.5°F. The pulse curve tended to lag behind that of temperature in some, while in others there was perfect correlation. The basal metabolism also showed similar correlation, the average increase being 20-25 p.c. which was in keeping with Vant Hoff's Law.[1] After the attainment of maximum values all metabolic disturbances decline.

The metabolic experiments provided an explanation for the widespread reaction, but they do not fully account for the increased excretion of sulphur, nitrogen, creatinine, potassium and phosphorus which have been demonstrated by control studies, nor is loss of body substance completely accounted for by the loss of muscle substance at the site of injury. There appears to be in addition to reflex wasting and autolysis a generalised increase in katabolism to meet exigencies of the enhanced metabolism of the recuperative forces. The nitrogen lost from the muscle only accounted for 4/5ths of the total weight loss.

The *metabolism of nitrogen in the surgical patient* was a subject of careful study by Brunschwig, Clark and Corbin[5]. The authors have studied the nitrogen balance in 40 cases subjected to a variety of major surgical procedures. They observed that a major surgical procedure with operative manipulation of deeply situated viscera and tissues, followed by brief period of starvation, and then gradual return over several days to ingestion of normal food constituents, together with complications often developing such as shock, fever, vomiting or the presence of injured tissue, altered the physiologic state because intake of nitrogen obviously could not equal the output. During this period a state of negative nitrogen balance existed for varying lengths of time. The cause of such increased katabolism might be due to 'toxic destruction of protein'.

The patients studied by them were under two types of post-operative management:—(1) Where the abdomen or thorax was not opened liquids were permitted by mouth as soon as tolerated and, shortly thereafter, a soft or regular diet was given ; the latter being by the third to the fifth post-operative day. (2) Where the abdomen or thorax was opened nothing was taken by mouth for the first 48-72 hours, fluids being given parenterally. On the third or fourth day small quantities of water were taken at hourly intervals, the next day clear liquids and, if tolerated, soft to regular diet was ingested by the sixth or the seventh day, except in operations upon the stomach where an increase in food by mouth was more gradual. Blood transfusions were not accounted for in calculating nitrogen intake.

Results of their findings are very instructive and are shown in the following tables, I and IA.

These data presented no correlation between age, sex, type of anæsthesia, presence or absence of malignant tumour or disease, and the extent of nitrogen loss. The most important factors were periods of post-operative starvation and limited food intake. Moderate brief rise in temperature did not affect the nitrogen excretion. Where the individual could tolerate food relatively early, and ingested a relatively liberal diet, there was a small net loss or even positive nitrogen balance at the end of the ten-day period. The day to day figures for nitrogen excretion revealed that the major portion of the net loss occurred during the first five days post-operatively when food by mouth was not permitted or was very limited.

METABOLIC DISTURBANCES IN BURNS.

Taylor and others[52], [53], [54] have discussed the metabolic disturbances in burns and they are of the opinion that the numerous underlying physiologic, metabolic and chemical complications must be constantly

TABLE I.

Net loss or gain in nitrogen in ten-day post-operative period in 41 patients undergoing a variety of major surgical procedures.

Operation.	*Patient.*	*Net N. Loss or Gain 10-day P. O. period.*
Thoracic sympathectomy	L.M.	— 27.10 Gm.
	MeM.	— 68.47 Gm.
Esophagoplasty	Ril.	— 75.17 Gm.
Exploratory celiotomy	Windb.	— 65.37 Gm.
	Bernst.	— 16.86 Gm.
	Valent.	— 3.81 Gm.
Acute appendieidis (peritonitis)	Ad.	— 49.17 Gm.
Gastric resection	Neh.	— 73.53 Gm
	Maz.	—175.79 Gm
Repair perforated peptic ulcer	Ly.	—136.06 Gm.
Cholecystectomy	Fish	— 24.34 Gm.
	Thomp	— 27.78 Gm.
	Miller	— 23.18 Gm.
	Lew	— 20.74 Gm.
	Barger	— 75.90 Gm.
	Patton	— 24.73 Gm.
	Bohl	— 68.65 Gm.
	Glynn	+ 5.91 Gm.
	Glayt	— 36.44 Gm
	Mal	+ 1.13 Gm.
	Pears	—114.09 Gm.
Radical mastectomy	Rawl	+ 1.23 Gm.
	Meed	— 15.68 Gm.
	Shaw	— 13.51 Gm.
Operation on extremities	Burdi	— 9.98 Gm.
	Kit	— 6.21 Gm
	Gal	— 30.00 Gm.
Thyroidectomy	Anth	+ 4.44 Gm.
Herniotomy	Berb	— 18.35 Gm.
Gastro-enterostomy	Hag	— 47.96 Gm
Partial colectomies	Robert	— 20.72 Gm.
	Boyer	— 60.22 Gm.
	Zaraz	— 51.86 Gm.
	Benk	— 49.48 Gm.
	Schr.	— 69.87 Gm.
	Ehl.	+ 4.97 Gm.
	Steph	— 41.44 Gm.
	Thomp.	— 59.88 Gm.
Operations on pancreas	Rapacz	— 39.96 Gm.
	Fait	— 24.41 Gm.
	Cullen	— 61.02 Gm.

TABLE IA.

Summary of data in Table I on nitrogen loss in ten-day post-operative period.

(A) Group ..I : 18 patients lost upto 40 Gm. of nitrogen average =21.31 Gm.
Group II : 7 patients lost 41 to 60 Gm. of nitrogen average =51.4 Gm.
Group III : 11 patients lost 61 to 175.8 Gm. of nitrogen average =89.45 Gm.
Group IV : 5 patients gained 1.13 to 5.91 Gm. of nitrogen average = =3.54 Gm.

(B) Calculated *dry weight of protein lost (Group I) = 133.19 Gm.; this represents +0.67 Kg. wet body tissue

Calculated * dry weight of protein lost (Group II) =321.25 Gm.; this represents + 1.6 Kg. wet body tissue.

Calculated *dry weight of protein lost (III) =549 Gm.; this represent +2.7 Kg. wet body tissue.

*Grams of excreted nitrogen × 6.65.

+Calculated on assumption that the relationship of tissue protein to water in the tissue is 1 :-5 (Best and Taylor: Physiological Basis of Medical Practic. 2nd ed Baltimore, Wilkins, pp. 915-916, 1940).

borne in mind. Frequently, the success or failure of carefully planned and well executed surgical procedures, such as skin grafting depends upon the early recognition and effective handling of these underlying disturbances. Infection, shock, anæmia and disturbances of kidney or hepatic functions are among those which are usually encountered. Presence of any one or all these factors may have profound influence on the metabolism of the patient.

Hypo-proteinemia.—The authors have studied a series of 63 cases in which hypo-proteinemia occurred frequently. In some, it was fugitive and was associated with early loss of plasma. In others it persisted for some time but was not severe and responded to high protein diet with Brewer's yeast. Yet another group would not respond to such diet since the burns were of more severe nature. In them hypo-proteinemia became progressive and often reached anasarca level. Simple loss of plasma in the form of persistent surface exudate could not alone account for the condition. In one case in which 55 per cent of the body surface was burnt, the urine nitrogen was occasionally as high as 3.4 gms. in 24 hours. At the end of six weeks he had sustained a net calculable loss of 2000 gms. of protein excluding that lost from the burnt surface. Significance of these figures is evident when one calculates that the loss equals as much as 40,000 c.c. of plasma expressed as loss of muscle tissue, this corresponds to loss of 10 kilograms or approximately 22 pounds. The patient however, responded to a diet very high in protein when the total nitrogen retention was over 6000 gms. of protein. During this time he had a net loss of 55 lbs. of original body weight.

Azotemia.—Authors have further pointed out that azotemia is a known complication of the severely burnt patient and two distinct types were occasionally observed. A reversible azotemia associated with transitory oliguria occurred frequently as an early complication. This phenomenon is similar to that frequently found following surgical operations and in shock, when oliguria or even anuria may persist for some hours. In this type, the restoration of normal urine output results in the return of increased non-protein nitrogen of the blood to normal. Since kidney can clear the urea at a definite maximum the condition can persist for a fairly long time.

Another type accompanied with hæmoglobinemia and hemoglobinuria occurred only in more severe cases, the causes of which are discussed by Shen *et al*[50]. The burns were of third degree and involved 20-55 per cent of the body. In such cases acid was excreted in the urine and azotemia in five out of six cases was irreversible. Non-protein nitrogen in these cases was not as high as was seen in renal shut down or complete anuria. It ranged from 80-100 mgs. per 100 c.c. of blood. Even after the restoration of normal urine output in such cases the N.P.N. of the blood did not return to normal.

It is understood that hemoglobinuria in acid urine might help the deposition of hemoglobin or its derivatives in the kidney[50]. And the damage of the kidney might explain the irreversible nature of the condition. But the fact that the total urine output was soon restored to normal in such cases showed that irreversible azotemia might result even in the condition of partial damage to the kidney. The excessive destruction of tissue protein might also be a contributory factor to high N.P.N. of the blood. The partition of the nitrogenous constituents of blood and urine (Table II and III) showed that in the former the portion of the elevated nitrogen was accounted for by urea but there was also a relatively large portion of undetermined nitrogen which was designated by some workers as 'Polypeptide nitrogen'[37]. In the latter also the higher level was accounted for by the excretion of abnormal metabolites or presence of a substance interfering with the action of urease.

TABLE II.

Partition of the Nitrogen in the Blood of a severely burnt patient.

Day.	Non-protein nitrogen mg./100 cc.	Urea Nitrogen mg./100 cc.	Creatinine Nitrogen mg./100 cc.	Creatine Nitrogen mg./100 cc.	Amino Acid mg./100 cc.	Residual Nitrogen mg./100 cc.
5	75.6	53.2	1.5	0.7	4.4	15.8
6	72.8	53.7	1.6	0.5	4.0	13.1
7	71.1	54.4	1.5	2.0	4.6	8.5
8	85	53.2	1.3	2.2	4.6	22.2
9	65.0	45.3	1.0	0.7	4.1	13.8
10	75.0	49.3	1.0	1.8	4.7	18.2
11	72.9	51.1	0.9	1.6	4.6	16.7

TABLE III.

Partition of the Nitrogen in the Urine of a severely burnt patient.

Day	Volume c.c.	Total Nitrogen gm.24hr.	Urea Nitrogen total%	Creatinine Nitrogen total%	Creatine Nitrogen total%	Amnio acid Nitrogen total%	Ammonia Nitrogen total%	Uric acid Nitrogen total%	Protein Nitrogen total%	Residual Nitrogen. total%
5	1520	8.0	43.5	5.5	0.4	0.9	0.8	1.1	9.6	37.8
6	1600	8.4	20.6	5.2	0.2	1.1	0.4	1.2	1.0	70.2
7	1140	7.0	7.6	4.9	0.0	1.2	0.7	1.3	0.0	84.4
8	1800	12.9	28.7	3.7	1.1	0.9	—	0.9	7.7	57.1
9	1490	11.2	10.0	3.0	0.3	0.9	1.6	0.6	6.3	77.2
10	1580	11.4	13.4	3.3	2.4	0.8	1.7	1.0	1.8	75.7
11	1970	13.9	5.0	3.0	2.7	1.0	2.9	0.6	2.9	82.7

The presence of hypoproteinemia has been seen by various workers [31, 38, 41, 17, 9, 21, 22, 41]. In a series of 81 patients 40 presented hypoproteinemia and there was correlation between the progressive type of hypoproteinemia and the severity of burns.

The fall in albumin and the reversal of albumin-globulin ratio was encountered early. It has been noted that the albumin level may remain constant while the globulin fraction actually rises. This rise may be frequently associated with infection and hepatic dysfunction. The hypoproteinemia was explicable on the basis of large amount of nitrogen loss in the urine which in some cases amounted to 45 grams per day as has been also observed by other workers[39]. In some cases the condition led to thyrotoxicosis[38]. Table IV shows some elucidative figures for the excessive loss of nitrogen.

TABLE IV.

Excessive total Nitrogen excretion expressed in grams per 24 hrs., in a severely burnt-patient.

	Days.																	
Hosp. No.	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1088906	6	17	9	32	9	10	7	13	9	10	11	7	4	8	9	10	8	9
1088895	—	21	22	9	21	25	17	18	19	45	19	13	28	28	38	9	10	13
1088910	13	16	18	17	—	26	23	14	15	12	11	2	14	15	4	24	21	16
1088930	10	20	21	—	15	11	25	5	8	14	10	10	11	11	12	11	11	16
1088865	—	—	22	—	5	13	14	9	11	12	14	8	—	3	16	10	8	15
1089011	—	11	18	10	15	17	16	22	19	19	28	16	—	14	17	16	14	14
1088976	—	22	23	9	17	16	26	11	14	13	17	21	8	9	—	4	16	11
1088892	19	—	34	23	24	30	26	9	30	11	11	24	26	20	19	14	13	20
1089013	—	17	9	12	17	8	14	18	13	14	18	17	19	20	25	24	22	19

The *EFFECT OF INFECTION* was investigated by Lyons[35]. He has observed the typical picture of chronic infection in surgical patients. There was weight loss, diminished strength and muscle mass, anorexia and anemia. The weight loss has been considerable ranging from 5 to 30 Kg. Muscle atrophy and loss of strength precedes weight loss and restoration of muscle bulk and strength appear prior to significant weight gain during convalescence.

The distribution of *extra cellular fluids* has been measured by the sodium thiocyanate[15], and Evan's blue dye method[27]. On admission to the ward the patients have had an interstitial fluid volume 4 to 7 liters too great for the standard of the patients observed, and weight significantly larger than the standard for the weight prior to injury. During convalescence interstitial fluid volume slowly decreased without apparent diuresis. The sedimentation rate has been correlated more closely with improvement than any other laboratory determination. Progressive weight gain is rarely apparent before the sixth to eighth week of convalescence.

Significant fluctuations in the *concentration of serum protein* and hemoglobin have been recorded. During the period of hemoconcentration urine volume may equal or exceed the fluid intake· Unless the blood volume is known a single observation of the concentration of serum protein or hemoglobin is misleading. Reductions of 1500 to 2000 c.c. in blood volume have been recorded. This degree of reduced blood volume is dangerous if it exists at the time of operation because minor blood loss may produce an ineffective blood volume and shock.

There is a *deficit of circulating hemoglobin* and there is normal or nearly normal quantity of serum protein. Fractionation of the serum proteins into albumin and globulin by the ammonium sulphate method in 30 cases failed to reveal any deviation from the normal. Plasma fibrinogen has been constantly elevated and there was no abnormality in blood electrolytes. It appears that major deficiency in chronically infected surgical cases is hemoglobin. This deficiency is often masked by hemoconcentration and normal or near normal quantities of hemoglobin in a given unit of blood. The accurate values are calculated only when blood volume is known. The prothrombin time was invariably normal. With normal plasma protein and elevated fibrinogen it was assumed that the liver function was normal. The penicillin therapy had no specific effect on the nitrogen, calcium and phosphorus balances but on the other hand positive nitrogen balance was not accompanied by restoration of normal hemoglobin unless penicillin was given.

The urinary nitrogen was fairly high in the series (15-20 gm. per day) without increased value of potassium.

Elman[19], [20], [21] has compared the metabolic breakdown after operation or burns to acute starvation and has considered only patients who were well nourished at the time of injury or operation.

When a healthy or well nourished individual sustains a serious injury or undergoes a serious operation, starvation always ensues. While *causes of such starvation* are those which lead to deprivation of one or more nutritional factors, there is another factor which increases the need for one of them. There is toxic breakdown of tissues which leads to protein deprivation even if the intake is normal and the diet well balanced. Similar in its effect is the normal loss of protein in discharge or exudates of one type or another, as in peritonitis, empyema, burns, damaged tissues or from large open wounds.

The diet requirements in such cases are usually inadequate due to several causes. Starvation is often imposed by the surgeon because he believes that ingestion of food will be deleterious. In some cases the patient is apprehensive. He is often permitted to take fruit juice or broth leading to protein insufficiency.

In another group of patients the starvation is due to loss of appetite which is frequently manifested after injury or operation, aggravated by sedation. Anorexia ends quickly in many cases but in some a vicious cycle is established by which the very effect of starvation becomes a further cause.

The *effects of starvation* are manifested in numerous ways. Loss of weight is the most evident outcome, yet its degree is not fully realised being masked by retention of water in some cases. In a brief survey by the author the loss of weight was enormous. One patient suffered a loss of 25 lbs. after an uncomplicated cholecystectomy.

The loss of weight may not be a quantitative measure of the degree of starvation because of the changes in water content which occupies 70 per cent of the body weight and are frequent and marked. This introduces a complicating factor. Nutritional edema may add several pounds to body weight and mask the loss of tissue. Secondly the loss of weight depends upon the depletion of two types of body tissue depots. Whether it affects fatty or protein tissue is of great significance. Physiologic impairment follows depletion of tissue including plasma protein whereas adipose tissue can be used without such impairment. Clinical significance, therefore, depends on the loss of protein rather than fat.

The loss of weight of protein tissue could be assessed by the estimation of nitrogen excretion. The excretion of nitrogen after injury or fracture is indeed enormous as has been repeatedly observed by the various workers. These quantities in terms of body tissue may account for the loss of as much as 1 to 5.3 lbs. per day. Loss of fatty tissue is comparatively less, of the order of 0.5 lb. per day.

There are many clinical symptoms which are seen in patients after an injury or an operation, such as fatigability and muscular weakness. These are due to loss of protein from the body. The observations have been corroborated by feeding a trained subject an iso-calorie breakfast. The most complete and convincing evidence about the influence of food on post operative asthenia was due to Mulholland and others[39] who showed that jejunal alimentation beginning immediately after operation alleviated most of these symptoms and accelerated convalescence in a series of gastric resections.

Nutritional edema is another serious clinical manifestation of starvation and may involve the gastro-intestinal mucosa producing severe symptoms including those of intestinal obstruction. This delays wound healing and is responsible for anemia or circulatory impairment. Other complications are lowered resistance to infections and hypoproteinemia.

A fall in the level of serum protein may be the first evidence of loss of protein from the body. This frequently escapes detection, since in some cases albumin is involved in depletion and many patients with hypoalbuminemia will show normal value for the total protein because of increase in the globin fraction. In some cases there is simultaneous dehydration which is responsible for normal values of serum proteins. Brown and others[4] have also discussed the metabolic aspects of the damage and convalescence. They pointed out that in healthy adult men after burns, fractures, wounds and operations there occurs a negative nitrogen balance lasting from 5 to 45 days. At the height of negative balance oral intake of nitrogen up to 100 gms. per day was followed by almost entire excretion of the same as urea in urine. It is, however, to be noted that intravenous administration of plasma was not thus excreted ; the nitrogen from casein hydrolysate behaved similarly to that administered orally.

The period of negative balance was succeeded by that of positive one. Intercurrent damage such as respiratory infection or fever was accompanied by increased excretion of nitrogen independent of food nitrogen. Similarly, a mild exercise for the first time such as wheeling around in a chair or changing the cot induced greater excretion of nitrogen. Persons, chronically ill before operation, behaved similarly but differed from normal individuals acutely damaged in that the raising the protein intake to moderate level diet did not lead to immediate excretion of the food nitrogen. These patients can thus be brought into positive balance at an earlier period and at a lower level of intake. Similar findings have also been reported by Riegel and others[46] in patients undergoing gastric or cranial operations.

Russel *et al.*[45] have shown that in shock after hemorrhage, the concentration of free amino nitrogen rises in the liver and the muscle. This is not due to inclusion of plasma of high amino nitrogen content, but the rise is mainly in the intracellular compartment. This confirms the previous indications of an increase in the rate of release of amino acids from muscle and show that in the liver the normal balance of formation and breakdown of protein is disturbed. The relative failure of the normal catabolism of amino acids also contributes to increase in plasma amino nitrogen.

Wang *et al.*[57] have worked on *the relationship of blood volume and mortality* in hemorrhagic cases.

The authors quantitative data showed that the residual blood volume at 50 per cent mortality (L. H. 50) is in the hemorrhage series, 59.1±2.9 ml./kg. body weight, whereas in the trauma series (L. H. 50) it is 73.4±3 ml./kg. body weight. The difference is statistically significant. This indicated that loss of circulatory blood volume alone was not adequate to explain the high mortality in traumatized dogs. They have early tachycardia, exceeding 200 beats per minute, high mean blood pressure, high hematocrit values, early depression of central nervous system, high peripheral resistance and high fluorescin circulating time.

SUMMARY

Thus various metabolic disturbances during surgery or burns have their origin in the process of tissue breakdown or more aptly, as some authors have put it, are due to toxic breakdown of body proteins. This condition in addition to setting free some toxic products in the circulation, brings about disturbances in the nitrogen metabolism of the body. The latter is recognized by abnormal excretion of the element in the urine in different forms. Owing to the unusual strain on organs concerned in metabolism, primarily the liver and kidney, other body functions such as the process of elaboration of plasma proteins, and hemoglobin, or the detoxication mechanism are disturbed. If the condition remains for a sufficient length of time the kidney function is damaged leading to further complications.

The metabolism of inorganic elements is disturbed mainly due to abnormal amounts of potassium set free from the areas of hemorrhages or burns, and loss of sodium from the body in the form of exudates. Soft tissues contain considerable amounts of phosphorus, and abnormal amounts of this in circulation affects the metabolism of calcium and magnesium.

The altered nitrogen and inorganic metabolism may perchance set up unbalance in other body functions such as the normal functioning of endocrine glands leading to serious after effects. The only successful measure to check these metabolic disturbances is to restore as soon, and as successfully as possible, the lost nitrogen from the body. Adequate protein nutrition therefore is of fundamental importance for rapid convalescence during surgery and burns.

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MEDICAL PRACTICE

PRIMARY ATYPICAL PNEUMONIA*

J. C. Patel §

During the past few years particularly since World War II, (1939-45) many of our ideas concerning pneumonia have undergone revision. Two factors are responsible for this change: (1) Development of highly effective means of therapy for certain of the bacterial pneumonias. (2) Intensive studies on disease of the respiratory tract during World War II served to differentiate primary atypical pneumonia from similar pulmonary infections of established bacterial, viral or rickettsial causes.

The occurrence of this disease in this counrty and all over the world has raised the question in the minds of clinicians as to whether this infection has made its appearance in man only recently or whether it escaped recognition previously. The disease did exist, but has now come to light, and is differentiated from bacterial pneumonia because of.—(1) Therapeutic response to sulphonamides and penicillin. (2) Improvement in methods of diagnosis of bacterial pneumonia. (3) Increase in use of X-rays in the diagnosis of chest diseases. (4) The results of virus studies in acute respiratory infections. (5) The studies carried out on respiratory infections in schools, colleges and camps.

The disease may have been mistaken in the past for influenza-grippe and more severe cases for bronchopneumonia to which no bacterial aetiology could be assigned.

In 1934 Gallagher[8] described a benign pulmonary disease occurring in a school among boys between the ages of fourteen and nineteen years. Most of the patients suffered from an upper respiratory disease before admission to the hospital. Pharyngitis was common but not severe. Headache, was frequent. Characteristically, the physical signs over the lungs were slight as compared with relatively extensive consolidation demonstrated by the X-ray. The pneumonic process started at the hilum and extended outward. Increase in pulse rate did not parallel the rise in temperature and the leuccocyte count was not elevated. The patients recovered without any sequelæ following a relatively short febrile course.

Gallagher[8] named the condition bronchopneumonia. Other names given to it are:—acute influenzal pneumonia, acute pneumonitis, acute interstitial pneumonitis, atypical pneumonia, atypical bronchopneumonia, virus or viral pneumonia.[9] The term primary atypical pneumonia—aetiology unknown, has been given by the United States War Office [16] and it is non-commital. It is called primary as the aetiology is unidentified, and it does not follow any other disease; atypical because the course of disease is different from that typical of bacterial pneumonia, Since Gallagher's[8] report, a number of authors [1, 2, 6, 11, 12, 13, 14, 16, 17, 19, 20, 21, 24] have reported the disease both from America and England [2], and the number of reports have increased since the beginning of World War II. Extensive reviews of the pertinent literature were published by Dingle and Finland[6] (1942) Mcleod [14] (1943), Owen [17] (1944) and Schmitz[21] (1945). During World War II the disease occurred commonly especially among the armed forces personnel. The disease has been described both in mild and severe forms, and occurred sporadically and in the form of an epidemic.

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* Based on a lecture delivered to the post-graduate students attending refresher course in tuberculosis on 2nd August, 1949, at J. J. Hospital, Bombay.

Whether the mild and severe cases are actually due to the same etiological agent is a matter of conjecture. However, studies of Kneelland and Smetna[11] and of Longscope[13] indicate that the severely ill patients may come down with disease following contact with mild cases and *vice versa*. It seems likely that most of the patients suffer from the mild relatively benign form of disease as indicated by the reports in the literature of epidemics.

CLINICAL FEATURES.

Relation to upper respiratory infections.—It is not clear whether the pneumonic process occurs in the absence of nasopharyngitis, but bronchitis is an almost invariable accompaniment, as evidenced by both clinical manifestations and X-ray examination. Pneumonia occurs in but a few of the total number of infections and in the great majority, the disease involves the upper respiratory tract without involving the lungs. It appears that an inflammatory reaction is generally present in the upper respiratory tract and that the lungs are involved either at the same time or secondary to the development of the upper respiratory process.

Incubation period.—The incubation period is as short as one or two days, or as long as three weeks or even longer.[9] It appears to be between two to three weeks on the basis of instances of natural case to case transmission [3 4, 5]. In experimental transmission of the disease to man the incubation period ranged from 7 to 14 days. If, however, pneumonia occurs in but a portion of the individuals who are suffering from the disease it would be impossible to assign an incubation period from the pneumonic form alone.

Symptomatology.—Primary atypical pneumonia is characterised usually by a gradual onset although in certain cases it may be abrupt. Chilliness, but not true chills, is common; moderate soreness of the throat is present and is more marked on swallowing. Nasal congestion, but no coryza, is present. Headache is very frequent, is usually frontal in distribution. There is a complaint that movement of the eyes is painful. In most cases cough appears early in the disease. This is paroxysmal and dry at first but becomes productive in 2-3 days. Sputum is mucoid or mucopurulant. Rusty sputum is not seen although it may be blood streaked in the early stages. Some patients with proved pneumonic involvement may go through the whole course of the disease, without producing sputum although cough may be present. Substernal soreness or aching in the chest may be present but pleurisy is absent. Malaise is not marked and is distinctly less than that associated with influenza or pneumococcal pneumonia. Profuse sweats may occur. Herpes is not seen.

Physical Signs.—The temperature is usually between 102° and 105°F, and may vary (from 99 to 106°F) considerably from day to day. In some, fever may be high and maintained; in others, it may be low. Duration of fever is[4] on an average, for about 10 days, with a range of one day to 6-7 weeks. The most common temperature curve is of the moderately remittent variety. Fever usually falls by lysis. Pulse rate is slow, considering the height of temperature. The respiratory rate is normal or only slightly increased. The soft palate and pharynx are congested and there may be hypertrophy of lymphoid follicles on the posterior pharyngeal wall imparting a coarse granular appearance.

The abnormal signs over the lungs are often scanty and usually the real extent of the pneumonic process is not recognized until rœntgenological examination is made. Evidence of frank consolidation is rare. The physical signs consist of slight impairment of the percussion note over the involved area, with presence of fine sticky rales which are best heard after coughing or at the height of a deep inspiration. In some cases rales are never heard at any time of the disease although in convalescence it is common for medium moist rales and rhonchi to appear.

Complications are uncommon and are rarely of significance. Pleurisy occurs rarely. Pleurisy with effusion has been reported. Acute sinusitis, otitis media, dermatitis, stomatitis, and gingivitis have been described. Thrombo-phlebitis, bronchiectasis and lung abscess has been reported. Hœmolytic crisis and anæmia have occurred.

Laboratory Investigations.—Cultures of the sputum do not show micro-organisms different from those present in the normal pharynx. Cultures of blood show no bacterial growth. Urine is normal Leucocyte count is usually within normal limits both as to total number of cells and distribution of all types. In certain of the cases reported by various authors a moderate polymorphonuclear leucocytosis occurred late in the acute phase or in early convalescence. The significance of this late leucocytosis is not clear but may perhaps be associated with a secondary bacterial infection in some instances. Positive cold-haemagglutination reactions (Peterson *et. al*, [18] 1943, Turner[26] 1943, and Turner and Jackson [27] 1943) are demonstrable with serum from approximately 55 per cent of patients. Both the frequency of positive reactions and the height of the titre which develop appear to be directly related to the severity or the duration of the disease. In severe cases or those with a prolonged illness, cold-hæmagglutination may be demonstrable in over 90 per cent of instances, while in mild cases the reaction may be positive in only about 20 per cent. The component responsible for this unusual reaction usually appears in the serum during the second week of the disease. Maximum titres are found usually during the third or fourth week and thereafter the titre gradually diminishes until eventually the component disappears. There is as yet no explanation for the development of positive cold-agglutination reactions during the disease. In the serum of the patient agglutinins develop against the Streptococcus MG in significant dilution in majority of patients (Thomas *et. al.*[25]) and this is now considered of diagnostic importance.

X-Ray Findings.—The discrepancy between the physical signs and the roentgenological picture has been emphasized by all those who have written of atypical pneumonia. The extent of the pulmonary lesion as visualized by X-ray is almost invariably much greater than would be expected from physical examination. Increase in bronchial markings is frequently seen characteristically. Consolidation appears first at the hilum of one or both of the lower lobes, whence it spreads out into the periphery of the lung fields. The shadow is not as dense as in the case of lobar pneumonia and has either a uniform ground glass appearance or may be patchy and diffuse with intervening areas of apparently normal lungs. Parts of one or more lobes may be involved. The lesion may advance in one portion of the lung while regressing at the original site Interlobar pleural thickening may occur. Pleural effusion is rare.

In some cases progression of the lesion outward from the hilum may not be evident but a generalised soft mottling may appear throughout a larger portion of one or both the lungs. It is not usually possible to co-relate closely the clinical severity of the disease with the extent of pulmonary lesions.

X-ray appearance may be mistaken for acute bronchitis, bronchopneumonia, cancer, early pulmonary abscess, lobar pneumonia, tuberculosis, acute bronchiectasis, psittacosis, American Q fever, primary coccidiomycosis.

Pathological Picture.—In the epidemic type of primary atypical pneumonia the mortality rate is extremely low and no pathological description of the lesions in these cases is available. On inspection the lung is crepitant with isolated areas of pink or grey consolidation that vary in size. There may be hæmorrhagic areas in the lungs. Often a thick exudate of mucous desquamated cells, monocytes and a few neutrophiles and eosinophiles fill the small bronchi, bronchioles and alveoli. Longscope[13] has summarised the histopathological findings in the lungs of patients dying of the sporadic type. The interalveolar septa are thickened and infiltrated with mononuclear cells. The alveoli contain loose exudate which consists of mononuclear cells, erythrocytes and coagulated serum. There is considerable œdema. The alveolar epithelium is swollen. The alveolar spaces in most instances are not filled either with œdema fluid or with exudate. The paucity of abnormal physical signs may be attributed to the fact that air remains in many alveoli and as a consequence alteration in the transmission in the sounds through the lung does not occur. The picture in these cases is of an inflammatory process which is essentially interstitial in character and, as in the case of certain virus infections of lungs in man and animals, is associated with a mononuclear cell reaction and hyperplasia of the alveolar epithelium.

DIAGNOSIS

Diagnosis can be made by (1) history, physical examination, laboratory examination and agglutination tests, (2) the roentgenogram, (3) absence of the therapeutic response with sulphonamide compounds and penicillin, and response to newer antibiotics—aureomycin, (4) by the process of elimination, which is the least desirable of the methods of diagnosis.

The more common clinical features are the following: gradual onset, remittent fever which is seldom high, pulse rate which is slow relative to the height of the fever, normal respiratory rate, cough slight or absent, physical signs of pneumonia and definite X-ray evidence of consolidation. Pertinent laboratory findings are the following:—normal leucocyte count, the usual array of bacterial species in the upper respiratory tract and sterile blood culture. Two laboratory procedures are of aid in reaching a positive diagnosis (1) cold hæmoagglutination test and (2) streptococcus MG agglutination test. Both are carried out with serum specimens obtained at weekly intervals during the course of disease. If either or both serological tests are positive and especially if a significant increase in either agglutination titre is demonstrable, some weeks after the onset there is a high probability that the diagnosis is correct. If both the tests are negative, it may be very difficult to establish the diagnosis.

Differential Diagnosis.—Primary atypical pneumonia can be readily differentiated from the common bacterial pneumonias. Clinical syndrome of atypical pneumonias can be produced in its essential characteristics by a variety of agents including bacteria, fungi, rickettesia and virus. An ætiological diagnosis can be established in these cases by the use of procedures, such as intradermal tests, isolation of the agent and immunological or serological tests with the patients' acute phase and convalescent phase sera. When positive results are obtained the illness must be considered as a pneumonia of specific ætiological type and diagnosis of primary atypical pneumonia should not be employed. Viruses of psittacosis, lymphogranuloma or ornithosis group, rickettsia of Q fever, and virus of influenza can cause picture simulating primary atypical pneumonia. However, all these known agents taken together accounted for an exceedingly small proportion of total number of cases diagnosed as primary atypical pneumonia. At times pulmonary tuberculosis, tularaemia, coccidiomycosis or toxoplasmosis may closely simulate the disease : so also may malaria, typhoid, undulant fever, tularaemia, fungus disease of the lungs, pneumonia produced by measles, influenza, chicken pox, vaccinia and variola.

EPIDEMIOLOGY.

This disease like many other infections occurs in epidemics and is spread by direct contact only rarely. Perhaps the causative organism is disseminated by carriers or diseased persons who are "moist speakers" or "impolite coughers". The disease is of widespread prevalance and although it usually occurs in epidemic form, small epidemics have been described. Epidemics have not been characterised by explosive outbreaks and attack rates have not been high. Usually they have occured among persons living under crowded or semicrowded conditions *e.g.* in school dormitories, military camps etc. The incidence in general populations is not known. In the army personnel incidence was greater than with other forms of pneumonia. The disease occurs at all seasons but is more common during cold weather. The disease occurs more commonly in the north temperate zones than elsewhere. It is prevalent but not common in the tropics[12, 24]. There is no particular predilection for age, sex or race. Infection is apparently transmitted by oral or nasal discharges of patients and the portal of entry is the upper respiratory tract. Second attacks have been observed [3, 4]. From this it can be inferred that persistant immunity against reinfection is not developed.

AETIOLOGY.

Despite many attempts to discover the infectious agent or agents there is as yet no complete agreement amongst investigators as to the nature and identity of the casual agents. Known bacteria do not cause it. Rickettsia and viruses known to cause other diseases in human beings are not responsible for it. The condition is similar to and has to be differentiated from infections with viruses or rickettsia of established identity *e.g.* pisittacosis (or ornithosis) virus, influenza A virus, influenza B virus lymphocytic choriomeningitis virus, rickettsia burnitti, etc. Inspite of thorough investigation by number of competent investigators, cause and mode of aetiology is still unknown. More than five different infectious agents each of which may be virus have been implicated as possible aetiological agents. Some of them have produced a disease simulating primary atypical pneumonia in some species of laboratory animals. In the serum of some of the patients, anti-bodies have been found by neutralising tests.

The results of experimental transmission of disease in human volunteers (Commission on Acute Respiratory Diseases, 1946) appear to have been more decisive than results obtained in laboratory animals. Sixty men were innoculated with pooled washings obtained from patients by nasal spray. Sixteen developed illness of primary atypical pneumonia. Other twenty six developed minor respiratory illness without pneumonia. Thirteen out of sixteen who developed pneumonia developed cold-agglutinins and two developed agglutinins against streptococcus MG. The Commission considers from the above results that the disease is at best initiated, if not caused, by a filter passing agent, presumably a virus.[4]

Thomas *et. al.*[25] sugested the possibility that a non-hæmolytic streptococcus, designated streptococcus MG, might be implicated in the pathogenesis of the disease. The bacteria were isolated from the lungs of fatal cases of the disease. The streptococcus is a single serological type of non-hæmolytical variety and produces a capsular polysaccharide which is responsible for the type specific immunological reactions obtained with it. Approximately 50 per cent of the patients develop agglutinins against streptococcus MG. If the disease is of short duration only 20 per cent of people, and if the course lasts longer, 75 per cent of cases, may develop agglutinins. These agglutinins develop in second or third week after the onset, commonly reach maximum levels during fourth or fifth week, and may decline somewhat during the seventh or eighth week. There is correlation between the severity of the disease and amount of agglutinin against streptococcus MG.

TREATMENT.

Before the advent of the new antibiotics[23]—aureomycin, there was nothing but symptomatic treatment for the disease. Aureomycin, when given to the patients of primary atypical pneumonia, produces rapid defervescence and decided clinical improvement.[7, 10, 15, 22] Schoenback and Bryer[22] reported a series of 18 consecutive patients suffering from primary atypical pneumonia which were treated with aureomycin. Prompt clinical improvement was noticed soon after the institution of aureomycin therapy. Temperature which was unaffected with penicillin or sulphadiazine came to normal within 24 hours in majority of cases. Meiklejohn and Shragg[15] have treated 22 cases of primary atypical pneumonia with aureomycin keeping a similar number as controls treated with penicillin. Comparision of the results by these authors showed that a substantial number of patients treated with aureomycin recovered soon after institution of therapy, and the protracted type of course observed in a number of penicillin treated patients was eliminated. All these reports conclusively show that aureomycin is effective in primary atypical pneumonia. Relapse might occur in some patients after stoppage of aureomycin, but the drug is as effective in relapse as in initial infections.

Dosage.—Shoenbach and Bryer[22] used a dosage of 40 mg. per kg. body weight and they gave 250 mg. every hour for first 3 hours followed by 250 mg. every 2 hours till the temperature was normal. Later the drug was given in the same dosage every four or six hours for 2 to 5 days. Meiklejohn and Shragg[15] gave aureomycin intravenously at the outset and followed later by oral therapy of 1 g. every six hours.

In both series nausea and vomiting were observed. Diarrhoea was observed in a smaller number of patients.

Apart from the above described aureomycin therapy there is no specific treatment. It has been claimed that chloromycetin, too, is effective in primary atypical pneumonia. There is no preventive treatment and despite isolation, the disease has been known to spread. Oxygen, at high pressure, is indicated in some cases with cyanosis and dyspnea. Symptomatic treatment for cough, headache, high temperature, generalised muscular aches, including backache, should be given. Fluids should be forced. Sulphonamides and penicillin are useless in the disease.

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CURRENT MEDICAL LITERATURE
MEDICINE

AETIOLOGY AND MODERN TREATMENT OF INFLUENZA. C. H. STUART—HARRIS. The Med. Press & Circular, 221 :75, 1949.

The influenza virus is not of a single species, but is a family of closely related species of viruses, and of these viruses the two important ones are the Influenza A and Influenza B, Whereas the A group has been associated predominantly with epidemics of Influenza, the B group has more often been associated with sporadic cases or small outbreaks. It is suggested that there is a dominance at one particular time of one member of the family of viruses over the remainder so that the human population which is affected by the infection, affords a suitable culture medium for the production of only one strain rather than the entire family of viruses. The study of epidemics is suggestive. They have tended to occur at every two to three years intervals in case of Influenza A and every 4 to 6 years in case of B virus. The longer the interval since the last major epidemic, the more likely it is that the next outbreak to be experienced will be extensive rather than localised.

Regarding clinical aspects of influenza, there has been no change since the recovery of the influenza virus. In the older, and chronically ill patient, there is more pronounced involvement of the respiratory tract with slower recovery, and in a small percentage of cases, true pneumonic involvement occurs.

The airborne nature of the disease defies sanitary measures and aerial disinfection by U.V.R. or other agents is impracticable. A polyvalent influenza vaccince is supposed to be potent and gives good immunity. It should not be given to individuals allergic to eggs. Children should be given the vaccine with caution as they are particularly prone to reaction.

Treatment of an established case remains the same as in the past, mostly symptomatic. Chemotherapy in influenza is still a matter for the future. Sulphonamides or Penicillin should be utilised when there are lung signs. If the patient does not respond to Penicillin, Streptomycin is the best form of therapy.

R. S. VELASKAR.

THERAPEUTIC CRITERIA IN RHEUMATOID ARTHRITIS. OTT STEOINBROCKER, CORNELIUS H. TRAEGER, AND ROBERT C. BATTERMAN ; J. A. M. A., 659-662 : 1949.

The first consideration in undertaking the treatment of a patient with rheumatoid arthritis is to determine the stage of the disease, the presence of rheumatoid activity and the degree of functional activity. The authors classify the following stages of rheumatoid arthritis.

Stage I—Early. There is no distinctive change on a radiogram. There may be evidence of osteoporosis.

Stage II—Moderate. X-Ray evidence of osteoporosis with or without slight subchondral bone destruction; slight cartilage destruction may be present. There are no joint deformities, though limitation of joint mobility may be present. Extraarticular soft tissue lesions, such as nodules and tenovaginitis may be present.

Stage III—Besides osteoporosis there is evidence of cartilage and bone destruction. Joint deformity, such as subluxation, ulnar deviation or hyperextension, extensive muscular atrophy may be present.

Stage IV—Terminal Stage. Besides Stage III, there is fibrous or bony ankylosis.

Regarding functional activity, the following classification is recommended. Class I—Complete functional capacity with ability to carry on all usual duties without handicaps. Class II—Functional capacity adequate to conduct normal activities, despite handicap of discomfort or limited mobility of one or more joints. Class III—Only little or none of the duties of usual occupation or of self care. Class IV is largely or wholely incapacitation with patient bed-ridden or confined to wheelchair, permitting little or no self-care.

With treatment, the stage of the disease rarely improves. However, either rheumatoid activity or functional impairment or both may improve. According to the Committee of the New York Rheumatic Association, rheumatic activity represents the crucial basis for assessment of the effectiveness of any therapeutic agent. From an idea of the functional impairment together with the criteria of response of rheumatoid arthritis to therapeutic agents one can have an insight into the influences of such general procedures as physical therapy, rehabilitative measures psychotherapy, orthopedic corrections, analgesic and constitutional therapy.

W. D'SOUZA.

CLUBBING OF THE FINGERS. A. W. BRONWOOD—EDIN. MED. J. 66 : 105-120, 1949.

Bronwood describes the groups, clinical features, significance, and mechanics of clubbing of fingers. Clubbing has been classified into three main groups, symetrical, unilateral and unidigital, and these may be acquired or hereditary. Acquired symetrical clubbing occurs in many types of respiratory diseases of which empyema, branchiectasis, lung abscess, bronchial carcinoma are the most important. It is not always present in pulmonary tuberculosis. Of the cardiac causes are congenital heart disease, subacute bacterial and rheumatic endocarditis and congestive cardiac failure. It may be also found in many gastro-intestinal diseases like carcinoma of the œsophagus, pyloric stenosis, tuberculous enteritis and regionalileitis, chronic dysenteries, idiopathic steatorrhoea, and in hypertrophic biliary cirrrhosis and amœbic hepatitis. Other causes of symetrical clubbing are enterogenous cyanosis, polycythaemia vera, purpura. Unilateral clubbing is seen in association with aneurysm of subclavian or innominate arteries or arch of the aorta, and pressure on sympathetic ganglia due to carcinoma of the apex of the lungs. Unidigital clubbing is very rare. It has been desribed in Boeck's sarcoidosis.

Clubbing of the fingers may begin at any age. The youngest child in this series was 3 years old. It is an asymptomatic phenomenon. The earliest sign is an increased fluctuation of the nail-bed which is rapidly followed by filling out of the angle between the nail and the basal tissues. The skin is stretched over this area. Alteration in the curvature of the nail then occurs. The nails become more brittle and grow more rapidly. Clubbing waxes and wanes with the activity of the primary disease and may disappear, when the causal condition has been cured. In the later stage, there may be enlargement of the ungual process and osteoporosis of the terminal phalanges. Both anoxaemia and toxaemia are important factors in the mechanism of clubbing. In congenital heart disease anoxaemia is the factor while in conditions like bronchiectasis toxaemia plays a part.

E. COELHO.

TREATMENT OF STATUS EPILEPTICUS, C. W. M. WHITTY AND M. TAYLOR. THE LANCET. 2 : 591-594, 1949.

The authors have found paraldehyde a drug of election in the treatment of status epilepticus. They recommend the following regime for an adult: Inject 8-10 c.c. paraldehyde intramuscularly into the gluteal muscle and massage the site of injection. Usually the fits stop within half an hour. If they do not, repeat 5 c.c. intramuscularly every half hour until they cease. Focal twitching without any tendency to spread does not need any sedation. If the patient's general condition indicates it, an intravenous glucose-saline or plasma drip is given. Paraldehyde may be added to this by intermittent injections into the drip tubing. Paraldehyde is soluble 1 in 8 physiological saline solution. Intravenous fluids are needed to combat dehydration and accumulation of metabolites in tissue fluids and blood. When the circulatory state of the patient is such that absorption of the intramuscular injection is doubtful the intravenous route should be utilised In children the dose is higher than is usually realised and even for infants 2-3 c c. of paraldehyde must be given to be effective. The paraldehyde need not be sterlised.

G. COELHO.

ON THE MECHANISM BY WHICH INTRAVENOUS INJECTIONS OF HYPERTONIC GLUCOSE SOLUTION CAUSE INCREASED CARDIAC OUTPUT. JAMES P. WALSH. Am. Jl. Med. Sc. 217 : 498-504, 1949.

The increase in the cardiac output after hypertonic glucose injection may be due to two factors. The hypertonicity of the solution may increase the blood volume and venous return and thus increase the cardiac output. As the extracellular fluid is more easily available in cardiac patients there will be greater and longer increase in cardiac output than in the normal subjects. The other factor is glucose itself which by improving cardiac nutrition will improve cardiac output. In 22 subjects in addition to repeated ballisto-cardiograms, blood volume, blood glucose, blood chlorides and venous pressure were repeatedly estimated after hyper tonic glucose injection.

There was slight rise in blood volume and venous pressure after the injection but this was so in normal as well as cardiac cases and could be correlated with either increased cardiac output or greater and sustained increase of output in cardiac cases.

Blood glucose increased significantly and remained so after the injection for the duration of experiment and hence glucose present in excessive amount may have caused increased cardiac output.

B. B. YODH.

DEATHS FROM VAGAL INHIBITION. KEITH SIMPSON, THE LANCET. 1 : 558-560, 1949.

The cause of sudden death has been an enigma since a long time. With the advent of the properly trained pathologist for autopsy work, causes of death with very little organic change like adrenal exhaustion, spasmodic hypoglycaemia, fat embolism, anaphylactic shock etc., have come to light. But there still remains a type of sudden death which occurs in an instant following some trivial action and autopsy fails to reveal any organic cause. The boey of status thymolymphaticus was raised in the times gone by by the pathologists who lacked the moral courage to deny absence of any organic lesion. From his series of 87 cases of sudden death Dr Keith concludes that death in such cases can only be due to functional failure. The vagus nerve enjoys a great deal of control over heart and circulation and the vagal center can be affected by a variety of stimuli from a large peripheral field. The reflex and direct stimulation of vagus producing inhibition of heart has been conclusively demonstrated in animals and is known to occur in human beings and it is the most likely cause of death in such cases.

With this view in mind some of the sudden deaths can be avoided by proper anaesthesia which will abolish the sensory part of the reflex arc, even for minor surgical procedures and by deferring such procedures during high emotional tension in the patient.

B. B. YODH.

LAURENCE-MOON-BIEDLE SYNDROME. A. K. NANDI, IND. MED. GAZ. 84 : 186-188, 1949.

The writer presents a very rare and typical case of Laurence-Moon-Biedle Syndrome which was first described in 1866. The characteristic features of this syndrome are :—1) mental weakness, 2) pigmentary degeneration of the retina 3) adiposo-genital dystrophy 4) poly-dactylia or syndactylia 5) familial occurrence. The case presented was a female, aged 15 years, brought for dimness of vision and lack of sexual development. Mother and father were healthy and not obese. One child had 24 fingers and toes. There was no abnormality in the other seven children. Physical examination showed obesity with distribution of fat on the cheeks, shoulders, breasts, abdomen, buttocks and over the mons veneris, and stunted growth and over-weight. There was no anaemia, jaundice, cyanosis nor oedema; no development of breasts nor genitalia. The hands were thick and spade-like and the skin smooth. One extra toe was present on the right foot. The intelligence was below normal. The field of vision was limited to the centre and night blindness was present. Fundal examination showed typical retinitis pigmentosa. Otherwise the C. N. S. was quite normal. The C. S. F. was normal. The C. V. S. was normal but for a pulse rate of 60 per minute & B. P. 85/65. B. M. R.—20. X-Ray. skull normal: right foot, supernumerary toe. The mental deficiency and poly-dactylia are thought to be of primary importance and a result of defective germ plasm, the other changes being secondary through involvement of the hypothalamus and indirectly the pituitary. This syndrome has not been recorded in Negro, Mongolian and Indian races. Of the 77 cases reviewed by Reilly & Lisser in 1932, the complete syndrome was found only in 25. Six autopsies reported pituitary abnormalities with striking predominance of basophil cells in the anterior lobe.

Treatment. The case was treated with oral and parenteral administration of Vitamin A for night-blindness ; in addition desiccated thyroid ½ gr. twice daily and anterior pituitary injections daily. Only 18 injections had been given, and so the results could not be judged. The only improvement seen was in the vision.

.C. SIMMONS.

MANAGEMENT OF PARKINSONISM : The Lancet. 1 : 572-573, 1949.

The general management is very important. These patients have to spend much more force for any action than an average person and hence their energy must be conserved. Regular exercises, moving all the joints, are essential. They may find riding a bicycle much easier than walking. Spinal brace may be helpful to correct the posture. Rigidity tends to be less in the evenings and this time may be utilised. They must be encouraged to pursue some employment as far as they can. Moderate social contacts may be allowed. As drugs, preparations of hyoscine and strammonium are very useful. They have to be pushed above pharmacological levels to gain maximum advantage. Parpanit is an antispasmodic drug and has al most similiar action as solanaceous drugs. Benadryl alone or in conjunction with other drugs is also helpful. It reduces the rigidity and prevents muscular cramps. Surgical procedures for relief of tremors have been tried but without much success.

Though we are on the track of new drugs the position of parkinsonian is not much better than it was ten years ago. It is deplorable that modest claims of scientific workers should be exaggerated in popular press raising false hopes of the patients and making doctors look as if they were far behind times.

B. B. YODH.

RETINAL & VASCULAR DAMAGE IN LONG STANDING DIABETES. J. H. Croom, G. I. Scott. The Lancet. 1 : 555-558, April, 1949.

Today diabetics live longer and the number of them showing degenerative lesions like retinopathy, arteriosclerosis, hypertension, intercapillary glomerulonephritis etc, have increased.

Whether diabetic retinopathy is a separate entity or a modified form of arteriosclerotic retinopathy is a controversial question. In the present series following criteria for diabetic retinopathy were employed (1) microaneurysms (2) haemorrhages which are usually deep and circular (3) small white exudates which tend to aggregate around macula (4) and certain amount of venous congestion. The criteria for arteriosclerotic retinopathy were constrictions at arterio-venous crossings, visible changes in the wall of the vessels, and irregularity of calibre or narrowing of arteries. With these criteria retinopathy was present only in 18 cases in a series of 60 cases of diabetes of 15—26 years duration. In nine cases there was no evidence of retinal arteriosclerosis and in the other 8 cases it was minimal. In this series there were 15 cases in which there was no evidence of any degenerative change at all.

These observations are in contradiction to the present belief that arteriosclerotic degenerative changes are inevitable in diabetes and no diabetic shall escape provided he lives long enough. It is likely that diabetic retinopathy is a separate entity and factors other than arteriosclerosis are responsible for it.

B. B. YODH.

THE ADRENOLYTIC ACTION OF DIHYDROERGOCORNINE IN MAN. Prof. R. H. Goetz, A. Katz. The Lancet. 1 : 560-563, April, 1949.

Dihydroergocornine (D. H. O) is an adrenolytic as well as sympatholytic drug. The injection of adrenaline after an injection of D. H. O. produced a fall in blood pressure instead of rise while the response of pulse rate, pulse volume, digital volume etc. remained the same. The respirations which became slow and irregular after the D. H. O. injection became normal on subsequent adrenaline injection. D. H. O. by itself produces slight depression of blood pressure and respiration and increase in cardiac rate. It does not promote destruction of adrenaline in vivo or vitro.

This drug may prove to be of some value in conditions where there is excessive outpouring of adrenaline like pheochromocytoma.

B. B. YODH.

THE EFFECT OF A HORMONE OF THE ADRENAL CORTEX AND OF PITUITARY ADRENOCORTICOTROPIC HORMONE ON RHEUMATOID ARTHRITIS. Preliminary Report. Hench, Kendal et alia (Mayo Clinic)—Proc. Mayo Clinic 24; 181-197, 1949.

The authors give a preliminary report of the results of treating patients with rheumatoid arthritis with the above hormones. The beneficial effects of pregnancy and jaundice on rheumatoid arthritis suggested that this disease was not microbic in origin, but was rather the result of some basic biochemical disturbance which is transiently corrected by some incidental biologic change common to pregnancy and jaundice. Various attempts were made by the authors to discover some biochemical denominator common to these states which might induce improvement in rheumatoid arthritis, but no certain clue was obtained. In time a conjecture was made that the antirheumatic substance might be an adrenal hormone. This conjecture was strengthened by the knowledge that temporary remissions of rheumatoid arthritis are frequently induced by procedures which are now known to be capable of stimulating the adrenal cortices, such as general anaesthesia or surgical operation.

Kendall's Compound E (17-Hydroxy-11-dehydrocorticosterone) was not available to the authors until September 1948, and its success in the first case in which it was tried was very striking. A woman with rheumatoid arthritis of 4½ years duration who was hardly able to get out of bed was given daily 100 mg. of Compound E by intragluteal injection. On the third day after the begining of the treatment she was able to turn freely in bed, and on the seventh day after, she went out shopping. After a reduction of the dose to 25 mg. daily the rheumatic symptoms increased.

The treatment has now been tried on 14 patients. Within a few days there was a marked reduction of stiffness of muscles and joints, lessening of articular aching or pain on motion, and significant improvement of function. The appetite often was rapidly improved and several patients gained weight. Compound E was given to 9 of the 14 patients for only 8 to 61 days. Then, unknown to the patients, injections of the hormone was abruptly replaced by injection of the control preparation, cholesterol. In 8 of the 9 cases symptoms began to return or increase promptly. The hormone has been given daily in varying doses to two patients for several months. The symptoms have remained controlled most of the time.

It is of course most unfortunate that the currently available amounts of compound E and andrenocorticotropic hormone are so small and will remain so for many months. Merck and Co. Inc., who have supplied compound E for this study express their regret that because of the exigencies of manufacture no supplies of compound E are expected for treatment or additional research until sometime in 1950.

E. J. BORGES.

NICOTINAMIDE AND SALICYLATES. La Presse Medicate No. 11, 154, 1949.

L. Rouques reports that Meneghini and Norza studied six patients who received 8 g. of sodium salicylate with 8 g. of sodium bicarbonate for 15 to 20 days. In all these, signs of intolerance of salicylates developed after two to three days of the treatment. After the sixth day they also received 0.4 of nicotinamide subcutaneously. They all benefited by the injections: the vomiting, the burning in the stomach, the eructations and vomiting all ceased. The level of the salicylates in the blood was not affected.

G. COELHO.

TRIDIONE—TOXIC EFFECTS. By Leard, Greer, and Kaufman. The New. Eng. Jl. of Med. 240, 962-966, 1949.

The authors report a case where leukemoid reaction in the sternal marrow and severe exfoliative dermatitis occured in a 69 years old man after the use of Tridione. He was taking 2 capsules daily for a month. There was a generalised macular haemorrhagic eruption. The spleen and liver were enlarged, the latter being tender. The bone marrow was hypercellular. The myelocytes and metamyelocytes were 65% of total leucocyte cells. The patient was put on a high carbohydrate, high protein, and high vitamin diet supplemented with Vit. B. He recovered in 32 days.

G. P. VARMA.

SURGERY

HIRSCHSPRUNG'S DISEASE AND IDIOPATHIC MEGACOLON: BODIAN, M., STEPHENS, F. D., & WARD, B. C. H. The Lancet. 1 : 6-11, J., 1949. Hirschsprung's disease has been described as a definite, separate entity from Idiopathic Megacolon.

Hirschsprung's Disease. The history begins at birth with constipation. The passage of the first meconium stool is delayed for several days. Constipation varies from one small stool a day to inability to evacuate for weeks. Gaseous abdominal distension develops within the first few months ; it may appear suddenly, may be accompanied by vomiting and present the picture of acute intestinal obstruction in the newborn, with tense, rounded, shiny, tympanitic abdomen. These attacks may subside with release of flatus . In severe cases passage of a flatus tube, bowel wash or laparotomy may be necessary. There is no abdominal pain. Stools are characteristic: very small pellets when hard, or thin tooth-paste like ribbons when soft. Defaecation is painless. The survivors of the precarious early days develop chronic abdominal enlargment and acute attacks of distension and obstruction may be superimposed. The distension is greatest in the upper abdomen, the ribs become flared and the diaphragm raised. *P. R.* shows a clean anus, a normal sphincter, well formed anal canal and a small empty rectum and perhaps spasm in the region of upper rectum.

Idiopathic Megacolon

Constipation is present in mild form from birth, but is overcome by mild aperients. There is no delay in the passage of meconium. Several years later more severe type of constipation develops. Abdominal distension is less marked and fæcal masses, as opposed to gaseous accumulations, are more apparent. Intestinal colic is common and is precipitated by purgatives. Borborygmi and flatus are less apparent in this group. The fæces are of larger diameter, hard and streaked with blood. Defæcation is accompanied by straining and sometimes pain. Because of pain the child holds back motions and accumulated fæcal masses distend the rectum. Soft and newly formed fæces are managed past this fæcal plug, causing a paradoxical diarrhoea or an overflow incontinence.

Radiological investigation with barium enema in the chronic stage of Hirschsprung's disease showed the rectum to be normal or less than normal in size. Above the rectum the diameter of the gut narrows for a distance which varies from 1″—12″. Above this it opens by a wide funnel into a highly dilated and gas filled colon. Idiopathic Megacolon showed simple colonic dilatation. It is divided into 2 sub-groups :—a) Terminal reservoir. When barium enema is given it shows that the rectum and distal pelvic colon form a pear-shaped unilocular dilated chamber sometimes extending from anus to xiphisternum. b) Tubular dilatation. In this the rectum appears large and the pelvic colon, which is longer and wider than usual lacks haustration, but the contour of the bowel is otherwise normal.

Pathology of Hirschsprung's Disease.

Neurohistological investigations on 15 cases have been done and have been supported by clinical and radiological evidence. The pathological findings in both intramural plexuses were uniform in all 15 specimens ; complete absence of parasympathetic ganglion cells was noted throughout the entire narrow segments. Moreover these aganglionic segments extended beyond the narrow bowel into the dilated part for 1-5 cm. On histological grounds, it cannot be stated whether this lesion resulted from degenerative changes. Circumstantial clinical evidence, strongly suggests a congenital lesion and the histology is compatible with the assumption of an agenesis of ganglion cells. This lack of parasympathetic function in the distal segment, accounts for the lack of co-ordinated propulsive movements. Unopposed sympathetic activity accounts for spasm in the distal segment.

Present Treatment of Hirschsprung's Disease is by rectosigmoidectomy. The workers conclude on clinical and radiological grounds that the distal narrow spasmodic segment is the primary obstruction and the dilatation and hypertrophy of bowel proximal to it are secondary. Hence by removal of this narrow segment, cases have been treated successfully.

Follow up of cases after rectosigmoidectomy, showed that the bowels act regularly, without constipation, abdominal distension or incontinence. No death occured in this series.

Suggested Management of Idiopathic Megacolon.

1) Thorough and repeated evacuation of bowels :—If the rectum is firmly impacted with hard fæces, these must be removed by hand under general anaesthesia. Colonic lavage is required daily until all fæcal masses are removed and then thrice weekly for 3 weeks and twice weekly for 2 weeks. Later weekly bowel washes should be given even if bowel action becomes normal. 2) Purgatives. After removal of the main bulk of fæces regular treatment with purgatives is initiated. 3) Education in normal bowel habits.

M. MASTER.

PRURITUS ANI : A study of Results with Gentian Violet in 210 cases. J. J. JENKINS, Am. Jour. Surg. **76** : 763-766, 1948.

The triphenylmethane group of dyes to which gentian violet belongs, are highly effective germicides even in dilutions of 1 in a million, against Gram-positive organisms, as also against monilia, torula, epidermophyton and trichophyton. It is also useful anthelmintic against thread-worms

In the 210 cases, threadworms were present only in 10% of cases In 70% of of the cases the pruritus occurred at night. The gentian violet was applied locally and administered orally, although by this route in one-third of the cases mild gastro intestinal upsets occurred. In all except 6 cases complete relief was obtained. The 6 failures included two cases of syphilitic ulceration and 4 cases who did not tak the treatment properly. In 20 patients there was recurrence of pruritus within 3 months ; all these responded to a second course of treatment. Any local ano-rectal lesions which might be considered as secondary causes were dealt with only after the pruritus was eliminated with gentian violet treatment.

E. J. BORGES.

PEDIATRICS

SALMONELLA INFECTIONS IN INFANCY. R. Clement. La Presse Medicale No. 10. 144-A, Feb., 1949.

Because of the biologic and pathologic relationship between the different organisms of typhoid, paratyphoid group, it is logical to put all of them under "Salmonella infections". Salmonella infection may be congenital, or acquired through contaminated milk, food, articles of clothing. In infancy typhoid fever is very often of the septicaemic type. Besides this, there is the colitis type with mucus in the stools, diarrheoic type, with watery stools, dehydration, and the prolonged pyrexial type—the pseudo-tubercular. Intestinal haemorrhage is rare. Encephalitis is common. When other organisms of the Salmonella groups are responsible for the infection, the clinical picture is different. Sometimes it is of alimentary intoxication, high fever, watery, foul smelling stools, abdominal distension, vomiting, loss of appetite. The commoner picture is one of prolonged pyrexia with relapses. The temperature is never very high. The stools may be profuse, watery, offensive, with prostration. Meningitis is common.

In the treatment of Salmonella infections streptomycin in a dose of 5 cg. per Kg body weight per day has been tried, but with inconclusive results so far.

G. COELHO.

RHEUMATIC CARDITIS IN CHILDREN. C. E. Thorton, The Med. Press Circular, 117-121, 1949.

It is probable that no child experiences an attack of rheumatic infection, even of the mildest type, without a coincident cardiac involvement. The child who has developed a rheumatic infection has, unless the infection is abnormally severe, a good chance of making a complete recovery with very little cardiac damage, provided the treatment is begun immediately and continued for a sufficiently long period. The foundation of treatment of rheumatic carditis is rest but, its organisation, even under hospital conditions, is by no means easy. The treatment is divided into four main stages.

Stage I—of absolute rest, where the patient is not allowed to do anything for himself but is nursed flat in bed with, at the most, one pillow. The length of time the child is maintained in this stage depends on the condition of the carditis. So long as it is active there is no relaxation of this stage.

Stage II—of recumbency. This is entered into when the carditis has essentially subsided. During this stage the child is allowed to feed himself, the number of pillows is increased to 2 and then to 3. The changes are made at fortnight intervals, and as soon as three pillows are allowed, he is permitted to read and write and made to wash himself.

Stage III—is sitting up in bed and is preparatory to being allowed to get up. Here all the restrictions are removed and the child is merely confined to bed. If everything goes on well this stage will not last more than two to four weeks. Formal teaching should begin now and massage· and bed exercises should be prescribed.

Stage IV is one of getting up. This is generally possible after three months of bed treatment. At the beginning the patient is allowed to be up for 2 hours. After a fortnight four hours are allowed. The child is kept on this for three to four weeks and an increase of 2 hours every fortnight is allowed till the child is up the whole day. During this stage musical drill and rehabilitation exercises are desirable.

The average duration of the treatment is 6 months, three months of which is spent in bed and three months in gradual resumption of a normal life.

The presence and degree of active carditis is assessed by the following :—

1. Sedimentation rate. This should be done at intervals of not longer than 15 days. So long as this is more than 15 mm. in one hour, the carditis should be regarded as being still active. When it is above 25 mm., the child must be kept in Stage I and when between 10 mm. and 25 mm. in Stage II.

2. The sleeping and waking pulse. An approximation of the two pulse rates is suggestive of active carditis. When the sleeping pulse is persistently above normal it is strong evidence of active carditis.

3. The cardiac physical signs. The variability of these signs rather than their presence is of importance. The lengthening and softening of an apical systolic murmur, the appearance of an intermittent mid-diastolic murmur and the sudden development of an aortic diastolic murmur are of significance. A gradual fading of all murmurs is a good indication of a subsiding carditis. An electo-cardiogram is helpful but is not essential.

4. Failure to gain, and loss in weight is suggestive of a smouldering carditis.

C. SIMMONS.

HOW CAN A NURSERY SCHOOL BE EXPECTED TO BENEFIT A CHILD? Barbara Biber. Jl. Ped. 34 : 112-119, 1949.

If the conditions are satisfactory nursery school experiences are very valuable in starting a child on the road to healthy growth and development. Whether the child should go to a nursery school and if so to which school must be carefully considered bearing in mind the following factors :—(1) the maturity of the child and his readiness to be separated from home, (2) the nature of home situation, (3) qualification and ability of the staff, and (4) physical set up and health standards of the nursery school.

During the nursery school period the child becomes aware of himself as an individual and as apart from other people. He developes attitudes in response to stimuli. In playing with other children, he learns the art of living with other people. He encounters restraint and authority, experiences denial and frustration, fear, loneliness, pain and anger, and struggles to adapt himself to the requirements of civilisation, toiletes, clothes, money etc.

The nursery school as an educational institution has an important function in helping young children in tackling major life problems of their early years and this is accomplished by a programme of experiences and activities provided therein. Of most importance is the psychological atmosphere created by the adults in the school. This consists of certain basic attitudes such as acceptance of the child as a person rather than censorship of his behaviour, desire to ascertain the motives behind his behaviour, awareness of irregularity of growth, and facility to nourish his first signs of independence without rejection of the needs of support and protection. The nursery school also helps him to enjoy personal vigour and learn the nature of physical objects in the surroundings. By continuously engaging himself with the objects in the nursery school, he develops his muscular cells and satisfies his desire for exploration It also helps the individual in his creative power.

The school offers a member opportunities to play and live together with other children. It is a source of joy to him. The child has a chance to widen his sphere of identification. He realises that he does not belong to one family but to a social group outside his home and gets initiated into a complicated social process by which individuals maintain themselves as acceptable and wanted members of social groups.

The play in the nursery school is symbolic and expressive of the fears, anxieties, and natures of the children.

Control and authority is vital to the growth of the child. One of the goal of the nursery school is to give the child experience with temperate authority. A child's mental health is conditional not only upon being loved, accepted, protected, but also upon having reasonable limits put upon his behaviour, being stopped from carrying to excesses some of his impulses, and upon being able to accept certain decisions. Severe punishments are never given, but the teachers make him know the reasons for what is expected, restricted and permitted. In exercising authority, it is the behaviour that is censured and rejected and not the child.

Children whose home conditions cannot provide minimum essentials like space to move about freely, children whose mothers go to work, and children of professional women should be sent to a nursery school.

K. J. Vyas

Sequelae of Infective Hepatitis in Children. Wyllie, W. G. and Edmunds, M. E. The Lancet. 2 : 553-555, 1949.

The authors review cases of twelve children aged 3½—12 years who suffered from infective hepatitis. Six of these died. In them the symptoms lasted from 11 days to 5 years. The liver, in the case of shortest duration, showed acute yellow atrophy. Subacute necrosis, with multiple nodular hyperplasia was the feature of cases of long duration. The classical portal cirrhosis was not seen in these cases. The authors observe that the clinical picture did not give any indication of the outcome, and ascites was not necessarily associated with a fatal outcome. There was no means of telling, during the initial illness, how an individual was going to fare. Liver function tests were not of much help.

G. Coelho.

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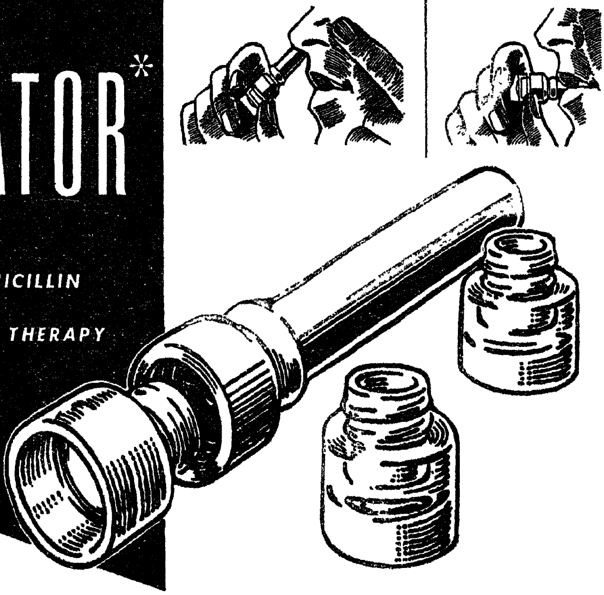

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MEDICAL ASPECTS OF ESSENTIAL HYPERTENSION§

A. Karmally*

Essential hypertension is a very common and important condition being one of the leading causes of death in cardiac disease. As the name indicates, hypertension is the essential feature of it. Clifford Allbutt described it as hyperpiesia. It is clinically characterised by a chronic and progressive condition in which there is a slowly continuous increase in blood pressure, first systolic and later diastolic, which progresses and remains for the rest of life. There is no known discoverable cause for it and one has to exclude causes of secondary hypertension which may be due to renal anoxæmic disease such as nephritis, pyelonephritis, tumours of the adrenal and pituitary, and coarctation of the aorta. No case of hypertension should be regarded as essential hypertension, especially in young individuals, unless co-arctation of the aorta, and renal disease with the aid of an excretory pyelogram are ruled out.

Diagnosis rests on the finding of an increase in the blood pressure. A few points in the technique of blood pressure reading may be briefly stressed. It should not be a hurried affair. The patient should get accustomed to his surroundings. The rubber band should be 12-13 centimeters wide; it should be carefully wrapped round the arm and not allowed to bulge out specially in fat arms. Raising the mercury rapidly above the level at which the pulse is not felt, releasing it very slowly, checking the systolic pressure by palpatory method so as not to miss the auscultatory gap, repeated readings to arrive at an average figure, avoiding taking of blood pressure immediately after meals are some of the points in this procedure that are worth emphasizing.

WHAT IS THE NORMAL BLOOD PRESSURE ?

The range of normal blood pressure varies with age. According to Wiggers,[6] upto 16 years the average systolic pressure tends to rise from 90 mm. of Hg. to 115 mm. of Hg. and diastolic from 60 mm. of Hg. to 75 mm. of Hg. At the age of 40 the upper limit of the normal is 140 mm. of Hg. systolic, and 90 mm. of Hg. diastolic. Above this age the systolic may reach 150 mm. of Hg. but diastolic does not exceed 90 mm. of Hg. 95 mm. of Hg. diastolic is suspicious and 100 mm. of Hg.

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§ Paper read before the Medical Congress, Bombay, 1948, in a Symposium on Hypertension.

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is always abnormal. Figures from the statistics of large American Insurance Companies state the normal pressure for the age of twenty to be 120 mm. of Hg. systolic to 79 mm. of Hg. diastolic and 134 mm. of Hg./87 mm. of Hg. for the age of 60. A plus or minus 10 percent for each age period should not be exceeded.

FACTORS REGULATING BLOOD PRESSURE

The blood pressure is maintained by various factors. Disturbance of any one of them may affect the blood pressure. The cardiac output maintained by the active and sensitive central pump, the elastic and accommodating large blood vessels, like the aorta, which keep up a continuous stream, and the arterioles which act as the sluice gates regulating the flow to the ultimate areas and maintain the peripheral resistance, are the factors which regulate blood pressure. Here, I may emphasise that the rise merely in the systolic pressure with a normal diastolic pressure does not connote the presence of hypertensive disease. The high systolic reading only should not be interpreted as diagnostic of hypertensive disease. These are merely systolic hypertensions which may be compensatory and as such need no treatment. In cases of bradycardia due to complete heart block, the large cardiac output raises the systolic pressure and a figure of 200 mm. of Hg. systolic, 80 mm. of Hg. diastolic is often commonly found. In arteriosclerotic disease of the large arteries, like the aorta in particular, due to rigidity and loss of elasticity, a further rise in systolic pressure occurs to compensate for the loss of the propelling force of the aorta. In a systemic arterial leak with a decreasing peripheral resistance, as met with in conditions of aortic regurgitation, arteriovenous aneurysm and patent ductus arteriosus the systolic pressure may rise with a low diastolic pressure. In nervous, highly strung, young individuals the systolic pressure may rise to 170 mm. of Hg. but the diastolic pressure may be only 80 mm. of Hg. I have stressed these forms of systolic hypertension as these are often diagnosed as essential hypertensions and energetically treated with the object of reducing the raised blood pressure, that is merely a compensatory episode. Essential hypertension is essentially a diastolic hypertension. It is one of the most common and serious type of diseases that one comes across in general practice. It has for its background an increase in the peripheral resistance, probably due to arterial vaso-constriction either of a generalised character or of renal vaso-constriction. Goldblatt's recent ingenious experiments of clamping the renal artery have stressed the importance of the rôle of the anoxæmic kidney in the production of hypertension. I will leave the pathological aspects to my colleagues to discuss. At present we know nothing definite to account for this important condition of essential hypertension.

ÆTIOLOGICAL FACTORS

Certain ætiological factors may now be considered. It is a disease of middle age and after. On an average signs appear, it is said, 10 years after the onset of sustained hypertension of a considerable degree. Its incidence increases over the age of 40. Heredity plays an important part. Families are known of whom several members have had hypertension with or without its effects. D. Ayman[1] made a direct study of the blood pressure of 277 familes to determine more clearly the presence of familial or hereditary factors in arteriolar hypertension. He grouped the families according to the presence or absence of essential hypertension, in one or both the parents. In families where both parents had normal blood pressure, the incidence of elevated blood pressure in children was only 3.1 per cent. In families with one parent having hypertension the incidence in children rose to 28.3 per cent. and when both parents had hypertension the incidence of elevated blood pressure in their children reached the level of 45.5 per cent. These results are strong evidence of a hereditary factor in essential hypertension. Robert Platt[5] who was interested in the study of heredity in hypertension, reported the family histories of 116 patients with a view to determining whether the cases without a family history of hypertension were those in whom hypertension was secondary to some demonstrable urological disorder. He has put forth his hypothesis that essential hypertension is a hereditary disease conveyed by a Mendelian dominant with a rate of expression of more than 90 per cent. The great majority of cases of hypertension which do not conform to this rule are not essential hypertension at all but are secondary to some renal or other causes.

A phlethoric type of build with a tendency to over-eating, and thickset builds are usually encountered in individuals; in whom high blood pressure is commonly found. Obesity and over-eating are frequently associated. A high protein diet is often blamed. Probably it is not the protein but the high fat diet which is responsible. Diabetes is another condition which is often associated with hypertension. Persons placed in responsible high positions with mental strain are more liable to it than those doing physical labour.

CLINICAL FEATURES

Essential hypertension usually manifests itself in the fourth and fifth decades. It is during this period of life that it is statistically more dangerous. When it occurs first in the fifties, sixties and seventies, its progress is generally slower. When it occurs in the third or fourth decade, it is a more rapidly developing disease and is frequently severe. We may divide the clinical course, which often is a protracted one, into three stages which merge into one another.

First, or the Early Stage.— There are really no symptoms and the high blood pressure is a chance discovery either in the course of a general examination, fitness examination, or an insurance examination. The blood pressure is labile tending to fall to normal at first especially during sleep. The increase is seen chiefly as on abnormal hypertensive reaction to emotion, fatigue and cold, and the systolic blood pressure is usually high. Diastolic blood pressure may show an increase but this is not much. Probably arterial spasm seems to be the immediate cause as this can be removed completely by rest, starvation and sedation. There are no physical signs. This corresponds to the Group I of Keith,[3] Wagner and Barker, who largely based their groups on ophthalmoscopical findings. Retinal changes are limited to narrowing or mild sclerosis of arterioles. Blood pressure is not excessively high and falls during sleep.

The Second Stage.—Here arteriolar spasm is greater and more persistent. Blood pressure is higher and more sustained. There are still no definite symptoms. Retinal veins are tortuous and nicked at arteriovenous crossings. Cardiac and renal functions are satisfactory. This is the Group II of Keith,[3] Wagner and Barker. The first two stages between them extend over perhaps two-thirds or more of the total duration of the cases of hypertension. During this stage various tests, *i.e.*, cold test and sedation test, may help to determine the amount of spasm present and therefore are helpful to a certain degree in assessing the suitability of hypertensive cases for sympathectomy.

The Third or the Final Stage.—This is associated with permanent irreversible organic changes occurring in arteries and arterioles supplying the important organs such as the heart, kidney and brain. No symptoms are present until complications set in and signs of cardiac renal and nervous failure appear. This pursues often a chronic course. It belongs to Group III of Keith,[3] Wagner and Barker where arteriosclerotic changes are more marked and angiospastic retinitis with hæmorrhages, exudates, or both are present. The blood pressure is very high and sustained and there may be dyspnoea on exertions, headache, nocturia, proteinuria and hæmaturia.

Sometimes in the third stage the clinical condition rapidly deteriorates and runs a rapid downhill course ending fatally. This is known as malignant hypertension with symptoms of excessive fatigue, headache, dimness of vision, loss of weight, dyspnoœ on exertion, nocturia, proteinuria, cylinduria, and hæmaturia. Retinitis is more diffuse and arterioles more sclerotic and in addition papilloedema is present. This is Group IV of Keith,[3] Wagner and Barker. Platt[5] considers that the benign and malignant varieties of hypertension are one and the same disease. He has put forth a plea for a change in the nomenclature of benign, to simple, and malignant which is invariably fatal, to compound in the same sense as these words are employed to interest on loans.

PROGNOSIS

Keith,[3] Wagner and Barker found that, three years after the first examination 20 per cent. of Group I, 36 per cent. of Group II, 75 per cent. of Group III and 90 per cent of Group IV were dead.

TREATMENT

Causal therapy being not feasible, a good deal can be done to ameliorate the condition of cases of hypertension by careful management. Very often the symptoms of the trouble start after the detection of a raised blood pressure in a routine or fitness examination. Headache, pain in the neck, and in the occiput, tired feeling, malaise, palpitation, are some of the symptoms complained of often after the detection of hypertension. These individuals begin to worry about their blood pressure and tend to develop a phobia concerning it. Actually the physician often unwarily makes the patient over conscious of the disease. I have known of cases where the mere detection of raised blood pressure has led to severe restriction of diet, absolute rest in bed, morning and evening taking of blood pressure, and abandonment of pleasure and work. The patients have become nervous wrecks whose only concern thereafter was the height of the mercury. A very undesirable state of anxiety is allowed to develop. It is the duty of the physician to gain the confidence of the patient. Every individual must be studied as regards temperament, amount of work, worries, rest, diet and other habits. He should be assured that many people suffer from this condition and they live almost a normal span of life, that with slight modifications he could lead a comfortable normal life. This psychological aspect of the case should be given more thought than has been bestowed on it so far.

Certain general rules to guide the patient would be helpful. *Rest and relaxation.* Night rest should be rather longer than usual, atleast a minimum of 8 hours. Holidays must be availed of, and week-ends must be restful. A 50 per cent. increase in rest with a corresponding reduction in activity will help considerably to diminish the load.

Diet.—Moderation in diet is an important item. In obese persons reduction in weight is desirable. Long continuous abstention from meat diet is not desirable and the use of lacto-vegetarian diet often leads to loss of appetite and anæmia. Recently Kempner[4] has advocated a diet which is known as a rice diet which contains no animal proteins and has a low sodium content of 0.15 gms. daily. Kempner observed objective improvement on this rice diet in two-thirds of hypertensive cases with or without demonstrable nephritis. A significant drop in blood pressure, a decrease in the size of the heart, improvement in electrographic findings and a return to normal of the level of nitrogen and cholesterol in the blood, were some of the objective findings. The diet being monotonous and non-appetising is difficult to be maintained for a very long time. It may prove of value when the patient is prone to attacks of pulmonary œdema or where œdema and congestion are resistant to diuretics and other forms of treatment. Alcohol in moderate doses does no harm and should be preferably taken after meals rather than before. Tobacco undoubtedly causes vasoconstriction in many people and so if it does not agree, it must be interdicted. Moderate exercise, short of producing pain or dyspnœa should be encouraged. Cold baths and swimming should be forbidden.

Drug Therapy.—No specific drug treatment is available. The time-honoured use of sedatives has been our mainstay in the treatment. Bromides alternating with luminal are very useful. Serpina apart from its sedative effect has no other credentials for its use. Nitrites have been used to lower the blood pressure. The small therapeutic dose that is used, has little effect on blood pressure. Moreover, the effects are temporary and short-lasting and their administration produces distressing symptoms of headache and gastric irritability. They are of limited value. They may be used temporarily during certain high blood pressure crises.

Thiocyanates are the drugs that effectively reduce blood pressure. The usual dose is 6 to 9 g. a day to begin with and half the dose after the first 5 or 6 days. The effective blood level is 10 mgm. per 100 cc. and should not exceed 15 mgm. per 100 cc. This needs frequent blood estimations, a great handicap in treatment. Toxic effects are very common and the toxic dose is very near the therapeutic dose. As the drug does not affect the cause of the disease, it is to be used continuously to maintain its effect on the blood pressure. Thus the remedy is of very little real practical value. It may be helpful for treating cases temporarily during a high blood pressure crisis or prior to sympathectomy. Other drugs like muscle extracts, tissue extracts, renal extracts have been used but with no definite benefit. Special symptoms like headache, convulsions, signs and symptoms of left ventricular failure have to be treated on the usual symptomatic lines. Recently surgeons have interested themselves in the treatment of essential hypertension. Removal of vaso-motor control by sympathectomy with lowering of the blood pressure has been undertaken in selected cases with favourable results. I leave this to my surgical colleague to deal with.

I thank you, Gentlemen, for having given me this opportunity to speak on a subject of common interest and importance to us all. I may once again stress the importance of the psychological aspect of the treatment. In these days of a faster and finer strung and more bewildering tempo of life than his autonomic nervous system is capable of serving at this stage of his evolution, man has unconsciously adjusted himself to this fast and hurried civil life. I may end by quoting Basset[2], : "The Psychological factor is a major barrier in the successful medical management of the majority of hypertensive cases. Most of them are at the peak of their productive years. It is neither psychologically nor economically sound; or in most instances, possible for them, to assume the role of a semi-invalid which is a requisite of good medical management.

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THE PATHOLOGICAL ASPECTS OF ESSENTIAL HYPERTENSION§

P. V. Gharpure*

The title of the subject as it stands needs careful definition. The word essential is defined in an English dictionary as something which is the "Chief point,"—may not be the only point. From this meaning of the word "essential" the title of this subject can embrace a variety of conditions. Dorland's medical dictionary defines essential hypertension as follows—"High blood pressure without antecedent inflammatory disease of the kidney or urinary tract." This is a preferable definition as it will enable me at any rate to restrict my remarks. With such a definition of essential hypertension the terms hyperpiesia and hyperpiesis proposed by Sir Clifford Allbutt as a designation for those cases of hypertension which are not due to evident renal or cardiac disease become synonyms with the title of our subject.

It has now been suggested that the term primary hypertension be preferred to the exclusion of secondary hypertension. The latter will embrace hypertension of renal, cardiac or endocrinal origin. Primary hypertension may be described to have two varieties—benign and malignant. These two may be entirely independent, the malignant not being the necessary sequence of the benign.

I may be forgiven for making this introduction as I wish to be quite clear as to what I am about to describe.

I am appearing before you after some lucid exposition by my predecessors. Dr. Karmally has done us the favour of defining the terms likely to confuse the issues and in a sense isolated the problem. Let me therefore proceed.

I propose to put the account before you in the following order.

1. The morbid anatomy of hypertension—autopsy studies and biopsy findings. (Personal and local data of autopsy work are not included as such inclusion will make the note too long).
2. Experimental production of permanent persistent high blood pressure and the applied physiology of the condition.
3. Experimental production of the morbid anatomical and histological changes comparable to those studied in the cadaver and with biopsy material.

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§ A note read in the symposium on the subject before the Bombay Medical Congress, 1948. Some illustrations of the histo-pathological changes in essential hypertension drawn by hand by Mr. Nadkarni, a third year student of the Grant Medical College were shown.

*From the Department of Pathology, Grant Medical College, Bombay.

I will place before you recorded facts verified experimentally and/or facts observed at autopsy or on biopsy. I would leave my listeners to think and discuss the application of these facts.

MORBID ANATOMY

There is a progressive hypertrophy of the cardio-vascular musculature differring in degree with age. The hypertrophy will be less marked if the coronary arteries are atheromatous. Even in benign hypertension the weight of the heart may be twice the normal. The left side dilates in a majority of fatal cases. The papillary muscle of the left ventricle markedly increases in bulk, the inter-ventricular septum bulges to the right and the left ventricle is lengthened.

Histology—the muscle fibres increase in size, the outline becomes indistinct, the myo-fibrillæ nuclei increase in size and appear more irregular. There is a diminution in the number of arterioles, small arteries and capillaries.

Johnson[8] first systematically studied the smaller arteries of most of the cases of chronic Bright's disease and described arterial hypertrophy similar to the cardiac hypertrophy. Gull and Sutton[11] stated that the changes in smaller arteries in hypertension were (1) hyaline, (2) fibrinoid, and (3) degenerative. Ewalds[8] confirmed Johnson's findings of hypertrophy. Jores[19] defined special vascular changes, a degenerative process in the intima, hyaline and fatty changes, hyperplastic thickening of the internal elastic membranes. Jores saw the changes in the smaller arteries of the kidneys, spleen, pancreas, but not in skeletal muscles except in one case.

Detailed studies of changes in the small arteries have been made by a number of workers—Fischer and Sehlazer[10], Fahr and Herheimer Evaens[7] and Fishberg[9].

The distinction between benign and malignant has been based on retinal changes by most workers—Michel[26], Karl[20], Coates[5], Leber[23], Vollard[31], Cohen[6], Keith-Wagner and Karnohan[21].

The stage of the disease, its nature—benign or malignant—and its possible further progress, it is now suggested, can be based on the findings of a pectoral biopsy removed after a local anæsthetic. In benign hypertension there may be no lesions in the peripheral arterioles or there may be moderate changes.

Clifford-Allbutt[4] considered dynamic narrowing rather than organic changes in the arterioles as the primary lesion. In spite of the diffuse pathological changes and marked arteriolar changes the retinal and cardia picture is long retained in a functionolly undisturbed state. It is possible that in these cases the duration has been short, or better compensation has set in, has taken place or is taking place.

In Malignant hypertension there is a definite type of retinitis. Cardiac enlargement and renal failure are prominent features. The blood pressure is usually high. Malignant hypertension is a terminal stage of the severe benign or the early malignant type. Basic changes are the same in both the benign and malignant types. The difference is one of degree only.

Changes in the arterioles of voluntary muscle are hypertrophy of the media, proliferation of the intima and marked reduction of the lumina. The normal ratio of the thickness of the wall to the lumen is 1 : 2. In this disease it may be 1 : 1 or 1 : 1.4.

Changes in the arterioles of voluntary muscle have been studied at necropsy and it has been confirmed that the changes are similar to those in other visceral arterioles.

The word arteriole is defined with reference to the size of vessels 25 to 100 microns. It is said that in the absence of arteriolar changes in the skeletal muscle there is "not a serious prognosis." The presence and the degree of such arteriolar changes indicate grades of seriousness. Karnohan *et al.*[22] summarise the subject of pectoral biopsy as an aid to the understanding of essential hypertension in the following words. "The arterioles in voluntary muscles of ambulatory patients with diffuse hypertensive vascular disease frequently show distinctive changes. These changes differ in degree and afford a valuable index for predicting the ultimate outcome in the individual case."

The above remarks apply to the prognostic aspect of clinical cases. Restricting ourselves to the subject of essential "primary hypertension" Johnson was the first to note the influence of minute blood vessels upon the circulation.

Mahomed[25] noted that the renal damage need not necessarily precede other factors. Allbutt, cited by Cowdry, confirmed this statement. This was an important step forward as till then the pathology of cardiovascular lesions had been influenced by the study of Bright[3] on the association of cardiac hypertrophy with renal disease. Landis[24] showed that the greatest pressure gradient in the mammalian was in the arteriole. Weiss[32] brought to notice the following—(i) the load of work on the arteriole is much more than on any other part of the vascular bed, (ii) arteriolar changes are relatively frequent in hypertensive conditions.

Karnohan, Anderson and Keith[22] introduced the study of the pectoral muscle. They studied arteriolar changes in the liver, pancreas, spleen and the gastro-intestinal tract and the pectoral muscle in autospy material and applied this knowledge to the study of pectoral biopsy. Normal control and pathological arterioles were studied with regard to their size, lumen, and coats. Four groups in order of severity have been suggested.

Briefly stated the changes in the arteries are :

A. *Hypertrophic changes*—hypertrophy of the muscle of the media, reduplication of the internal elastic lamina, a notable development of new musculo-elastic layers in the arteriolar walls and proliferation of the sub-endothelial connective tissue accompanying all varieties of sustained arterial hypertension.

B. *Degenerative changes*—(i) Diffuse fibrosis in small arteries. (ii) Fibrinoid degeneration in arterioles. (iii) Acute arteriolar necrosis.

I will omit detailed reference to the 4 groups as Dr. Karmally has dealt with a grouping of a similar kind on the basis of clinical *cum* pathological considerations. However briefly these 4 groups are

GROUP ONE

Benign hypertension—

B. P. systolic definitely and persistently at 140 mm. Hg. No evident cardiac or renal damage.

Retinal arterioles—minimal degree of sclerosis.

Arterioles of the pectoral muscles—ratio of thickness of wall to diameter of lumen reduced.

May remain stationary or may progress to more severe forms of hypertension.

GROUP TWO

More marked ratio of wall to lumen ; more pronounced retinal arteriolar sclerosis but no retinal, cerebral, cardiac or renal insufficiency. Systolic B. P. higher than 200 mm. Hg.; termination—cerebral thrombus.

GROUP THREE

Marked hypertension ; more pronounced arteriolar sclerosis in retina ; functional changes—cerebral, cardiac, renal; ratio of wall to lumen 1 : 1.4.

GROUP FOUR

End-phase or a distinct entity.

From these recent studies it may be said that pectoral biopsy holds out a promise to the better understanding of the state, stage and the possible termination of a given case of essential hypertension.

EXPERIMENTAL STUDIES ON THE CAUSE OF HYPERTENSION

The relation of the kidney to hypertension was demonstrated early, as far back as 1836, by Richard Bright. Subsequently pathologists undertook the study of the problem in animals. Without going into details of the numerous experiments it will suffice if the conclusions of experimental work are briefly stated.

(i) Bilateral nephrectomy fails to produce hypertension.

(ii) Diminution of the amount of functional renal tissue, *e.g.* destruction of renal tissue by X-Rays, may produce a moderate elevation of blood pressure.

(iii) Occlusion of one renal artery produces temporary rise of blood pressure.

(iv) Occlusion of both renal arteries ocasionally produces moderate to severe hypertension.

(v) Permanent obstruction of ureters produces rise of blood pressure. Harry Goldblatt *et al.*[13] have substantially added to our knowledge of the origin of hypertension by experiments on animals. In a few words their conclusion is that for the production of hypertension the kidney must remain in the body and be partially deprived of its blood supply.

An extra-renal hypothesis was built up which assumed that the arteriolar hypertonus was the result of sustained overactivity of the sympathetic nervous system. This hypothesis became the basis for the surgical removal of part of the sympathetic nervous system, and a series of elaborate surgical techniques were devised with the object of releasing as many arterioles as possible especially those in the splanchnic area, from sympathetic control. These are—

(i) Denervation of the renal pedicle (Page [28]).

(ii) Section of the splanchnic nerve and excision of the lower four thoracic sympathetic ganglia (Goldblatt *et al*[13]).

(iii) Section of the anterior nerve roots from the second dorsal to the second lumbar inclusive (Goldblatt and Wartman [14]).

(iv) Excision of the entire sympathetic nervous system of the thorax and abdomen, including cardiac denervation (Freeman and Page, Alpert, Alvin and Grimson[1], Hymans *et al.*[16]).

The results were occasionally brilliant but often disappointing and not often permanent. They have received no experimental support. Experimental work planned to study the rule of the sympathetic (extra-renal) factor in hypertension has produced results which negative the suggestion of the nervous origin of hypertension.

Houssay and Fasciolo[17] were the first to provide experimental evidence to show that primary hypertension is not initiated by a nervous reflex from the ischæmic kidney but it is due to the production in the ischæmic kidney of a chemical substance having a pressor action. It is possible that this pressor substance acts on blood pressure through the agency of one or more of the ductless glands.

Page and Sweet, Blacklock[2] and Levy and others have worked on the role of the endocrine organs. One of their conclusions is that it is the adrenal cortex and not its medulla which is essential for production of essential hypertension.

In the above brief account is described the subject of experimental production of hypertension. The production of arteriolar changes experimentally has also been achieved. In Goldblatt's experimental animals arteriolar changes were not constantly observed. Wilson and Byron[33] by planned experiments in rats, have successfully produced arterial degenerative changes. The arteriolar changes were widely spread in viscera in some of his animals.

There is one other aspect to which reference may be made—humoral mediation of hypertension in renal ischæmia. The pressor substance elaborated by the ischæmic kidney is known as renin. Normal blood contains a substance known as renin activator that is used up in the process of inducing hypertension. The interaction of renin and renin activator produces a substance, angiotonin a crystalline substance, injection of which into intact animals produces a temporary rise of blood pressure and in nephrectomised animals and in animals with ischæmic kidneys gives a more marked response. It is possible that the serum of a normal animal contains a inhibitory substance, angiotonin inhibitor. It is also possible that a renin inhibitor substance exists. Page and Helmer[29] consider that the substance angiotonin activator is necessary for action of angiotonin

If at least some cases of human hypertension are caused by the development of excess of renin by an ischæmic kidney it follows that an injection of angiotonin-inhibitor contained in extracts of the kidney should be of value in treatments. The results reported by Page, Helmer, Gambill, Taylor and others have been encouraging.

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OBSTETRIC ASPECTS OF ESSENTIAL HYPERTENSION§

H. V. Tilak*

INTRODUCTORY

In Obstetric practice, blood pressure over 120 mm. Hg. systolic and 80 mm. Hg. diastolic detected before, or in the first twenty weeks of pregnancy and not associated with chronic nephritis is called Essential Hypertension. In America 140 mm. Hg. systolic and 90 mm. Hg. diastolic before, or in the first 24 weeks of pregnancy is taken as the lower limit of Essential Hypertension, but F. J. Browne of London who has observed a large number of these cases for many years is of the opinion that if a woman has a blood pressure over 120/80 mm. Hg. even once before, or in the first 20 weeks of pregnancy, she should be kept under observation and treatment as a case of essential, or, what he calls Chronic Hypertension. It has been found that in normal persons the blood pressure does not rise with age. Browne holds that even if blood pressure rises occasionally and comes down to normal after rest it is still a case of Chronic Hypertension because many of these cases are found to show increase in blood pressure during pregnancy and it does not decrease for many months after delivery.

The proviso that hypertension must have been observed before, or in the first 20 to 24 weeks of pregnancy is put because pre-eclamptic toxæmia which it closely simulates is rarely observed before this period and therefore if a woman is not suffering from chronic nephritis the condition is Essential Hypertension. If the urine shows albumin or there is œdema of the limbs, ophthalmoscopic examination and kidney function tests, such as urea or phenolsulphonthalein excretion tests, should be done to exclude chronic nephritis. If the hypertension is first observed after the 20th week of pregnancy it is difficult to differentiate essential hypertension from toxæmia because in both the diseases rise in blood pressure, urinary and eye-ground findings are more or less similar. It is by keeping the case under observation that we find that in toxæmia, œdema and the amount of albumin in urine dominate the picture, while high blood pressure is the predominant sign in essential hypertension. The blood pressure usually rises in the last three months of pregnancy. After delivery, the blood pressure comes to normal in a few weeks in almost all cases of toxæmia, but in essential hypertension it remains high for nearly a year. It must, however, be noted that in nearly 30% cases of essential hypertension, pre-eclamptic toxæmia and even eclampsia supervenes in the last 3 months of pregnancy. This makes differential diagnosis difficult and prognosis unfavourable.

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The blood pressure in essential hypertension is only a sign of generalised spastic contraction of the arterioles. It is confirmed by eye-ground examination which shows localised or general spastic contraction of retinal arterioles. Albuminuric retinitis is not seen unless the disease is advanced.

ETIOLOGY AND VARIETIES

The main causative or contributory factor of the disease is worry or mental distress and the treatment is directed to the relief of this factor. In a few cases it runs in families. Pregnancy itself causes this disease in some women.

Essential hypertension can be conveniently divided into benign and malignant varieties. Benign cases (blood pressure upto 150 /90) are seen fairly frequently during pregnancy. Browne finds them 4½ times as frequently as chronic nephritis in pregnancy. Chesley and Annitto find that one-third of the cases classed as late toxæmias are cases of essential hypertension.

IMPORTANCE OF ACCURATE RECORDING

I could not get records of cases of Essential Hypertension from any of the big Maternity Hospitals in Bombay. There may be three reasons for this. Firstly, cases usually go there for registration after the sixth month of pregnancy when, as I have stated before, the disease is difficult to differentiate from pre-eclamptic toxæmia. Secondly, cases of Malignant Hypertension which can be readily diagnosed in any period of pregnancy are rare in obstetric practice as it is generally found in women of 40 years or more, when pregnancy is rare. Thirdly, mothers do not care to attend the clinic sufficiently long after delivery, when only it is possible to verify this disease. I or my colleagues have not so far maintained a record of cases of Benign Hypertension as they do not worry us but malignant cases arrest our attention. I recollect only 3 such cases and my colleagues have kindly given me records of 6 cases they remembered in their practice. This shows that cases of malignant hypertension uncomplicated by toxæmia of pregnancy are very rare in Bombay.

Here I would like to observe that time is now ripe for enlarging the scope of work of the ante and post-natal departments of large Maternity Hospitals where students are being trained. There is usually a separate staff for examining the mothers and keeping records. The authorities should encourage mothers to attend the clinic right from the 2nd month of pregnancy, and from then on till a year after delivery. This will make it possible not only to detect early cases of Essential Hypertension and Chronic Nephritis, but to prevent and treat cases of early toxæmias and abortion. I would also appeal to the authorities to maintain a uniform method of keeping the records so that they can be compared and pooled together for purposes of study.

COURSE OF THE DISEASE

A large majority of cases of Benign Hypertension go through the pregnancy without appreciable harm to mothers or babies. Chesley and Annitto found slight albumin in urine in nearly half of their cases but in nearly 93% of them the kidney function was good. In the borderline cases with the blood-pressure rising to 160/100 mm. Hg. there is a possiblity of abortions, still-births, and ante-partum bleeding. According to Browne this is due to spastic contraction of arterioles in the decidua leading ultimately to the death of the foetus. In Malignant Hypertension with blood pressure rising to 220/150 mm. Hg. the mother suffers from severe headache and insomnia, and there is a greater tendency for toxæmia of pregnancy to supervene. In such cases the maternal mortality is about 12% and nearly half of the foeti die in utero or soon after birth. Other workers have not found such a large percentage of deaths

TREATMENT

I shall restrict myself to the treatment of these cases during pregnancy. They require periodical examination of the urine and of the eye-grounds. Rest is important. Bromides and barbiturates are good for insomnia and nervousness. Vitamins and salts of calcium and iron are indicated particularly when the diet is poor in nutrition. The use of table salt and fats should be restricted and sodium bicarbonate should not be given for heart-burn as it leads to retention of water in tissues. If the blood pressure has a tendency to rise, daily intravenous injections of 250 to 500 cc. of 20% glucose are recommended by Green Hill. They relieve the spasm of the arterioles, produce diuresis and reduce blood pressure, headache and œdema. If the patient is anæmic, examination of the blood and stools is necessary to find out the cause and to institute appropriate treatment. I have found casein hydrolysate useful in cases of Hypertension with œdema.

The treatment of Malignant Hypertension is practically the same as that for Benign Hypertension but as there is greater danger to the mother and the foetus, pregnancy should be terminated by inducing labour between the 36th to 38th week, or earlier if there is toxæmia. The fœtus is usually undersized in these cases, but it does not stand compression by the cervix or perineum. Browne advises high rupture of membranes to keep the bag of waters intact, and episiotomy if the advancing head is found even slightly compressed by the perineum.

If we look to the treatment of pregnancy toxæmias we find that it is practically the same as that for essential hypertension. This shows that a common factor is operating in both the diseases during pregnancy and that factor is angio-spasm. It has been emphasized by many workers in the last few years, that spasm of arterioles is the main factor in late toxæmias of pregnancy. The cold pressor test done in early pregnancy also points to the same factor. In 50 % of the mothers in whom the test is positive either essential hypertension or late toxæmias of pregnancy are found.

ANALYSIS OF CASES

The salient points in the 9 cases of Essential Hypertension collected by me were the following :—

All the patients were multiparas. In two there was history of eclampsia in their first pregnancy. One had essential hypertension in her family. Only one case showed a trace of albumin in the urine. All others had no albumin and no œdema. The blood pressure varied from 160/100 to 210/150. There were 14 abortions, still births, or neo-natal infant deaths in the 9 cases, one case had ante-partum bleeding, two of the cases died of cerebral hæmorrhage 2 or 3 years after their last delivery. One case had hæmoptysis throughout pregnancy, but she gave birth to a healthy baby after induction of labour with high rupture of membranes. In one case Cæsarean section was done as her last baby died of convulsions soon after birth.

OPHTHALMIC ASPECTS OF ESSENTIAL HYPERTENSION§

S. N. Cooper.*

In the common ground on the subject of hypertension between the physician, the surgeon, the cardiologist, the gynæcologist and the ophthalmologist, the ophthalmologist has played no small part in a more correct, clear and intelligent understanding of this cardio-vascular-renal-retinal condition.

The essential and initial changes, as we shall see, take place in the arterioles of the kidney and nature writes these changes in the blood vessels of the retina in heiroglyphics for those who can decipher. The ophthalmologist is placed in the enviable position of being the only one who can read this nature's language with the help of the mysterious light in his ophthalmoscope, and has earned for himself an important role in working out the present conception of this important clinical entity as well as its diagnosis, classification and prognosis.

Anatomy.—Briefly speaking when we see the retinal arteries with an ophthalmoscope we are not looking at the retinal arteries but the retinal arterioles. An artery has an intima which is composed of an endothelial lining and an elastic lamina which forms a wavy homogeneous layer underneath the endothelium. Outside this is the tunica media which is composed of a thick coat of several layers of musculo-elastic tissue, outside which is the outermost coat, the fibrous tunica adventitia In the arterioles the intima consists of only a single layer of endothelium without the elastic lamina, the tunica media is reduced to a single interrupted layer of thin smooth muscle fibres, and the adventitia can only be seen at the arterio-venous crossings, where there is a common adventitia for the arteriole and venule.

When we look at the beautiful vascular tree of the retina with an ophthalmoscope, it is only the first divisions of the central retinal artery that bear the structure of an artery. From the second divisions onwards the structure rapidly changes to resemble that of the arterioles just described. The pathology of changes that affect the arterioles can therefore be seen from the second divisions of the retinal vascular tree onwards. These retinal pipes which carry blood for the inner layers of the retina have transparent walls with the same refractive index as the retina and are therefore invisible, so that if they were not filled with blood one could not see them with an ophthalmoscope. They can only be seen when filled with blood, the blood column being a cast of the lumen of the vessels, and any variation of the blood column will be an exact measure of the changes in the lumen caused by the changes in the tunica media and intima. Although the surrounding tunica media is not visible its presence and condition can be appreciated by the reflection from its cylindrical surface. Any cylindrical object *e.g.* your fountain-pen if you hold in front of you will show a bright streak running in the centre. (Plate I). If we take a narrow test-tube the light streak on it will be narrow, but if a broader test-tube is taken the light-streak will be broader. If we take the narrow test tube, fill it with a red fluid an insert it in a broader test-tube filled with water, the red column of fluid will appear to be in a test-tube with a thicker wall a condition which simulates exactly what takes place in thickening of the vessel-wall. Here the light-streak becomes broader, and the blood-column remains narrow. If the wall of the test-tube were made of glass with a higher refractive index than ordinary glass, the reflected light-streak will also be brighter. In spite of the transparancy of the vessel-wall therefore, we are in a position to judge the state of the tunica media by the reflection from the surface of the cylindrical vessel-wall, a brighter light-streak will indicate an increase in the density of the vessel-wall as takes place with hyaline degeneration of the wall.

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The fibrous tunica adventitia is usually absent from the retinal arteries and arterioles, but often it may be present along the first divisions of the retinal arteries in which case a thin white sheathing of the bigger retinal vessels may be present which soon disappears as the vessel subdivides and thins out, and may be considered a normal phenomenon.

At the arterio-venous crossings in the retina if we look at a typical section, we find that the endothelium of the venule lies directly on the outer surface of the tunica media of the arteriole surrounded by a common adventitia, a feature duplicated nowhere else in the body except in the afferent and efferent vessels of the kidney glomeruli. A study of the arterio-venous junctions of the retina is of particular importance in the study of hypertensive vascular disease as the changes in the vessel-walls that take place can be read mostly at the crossings.

Through an ophthalmoscope a normal arterio-venous crossing will show the following features:

1. The vessel being transparent, the vein that passes beneath the arteriole can be seen through the overlying vessel.
2. The vessels cross each other without any change in direction.
3. There are no signs of compression of the venule by the thicker arteriole.

In the role an ophthalmologist has to play in the understanding of this cardio-vascular-renal condition, he with his ophthalmoscope can discern the exact changes taking place in the retinal arterioles and at the arterio-venous crossings, and so is in a position not only to diagnose an early case but to place a given case in its proper group I, II, III, or IV. He can pronounce an accurate prognosis of a case of essential hypertension, and in the hypertension of pregnancy he has a large say in the important decision about terminating a pregnancy, and whether such a case be allowed to conceive again or not.

With this responsiblity on his shoulders let the ophthalmologist now peep into the hidden chamber behind the pupil. He looks at the blood vessels. He looks at (1) the blood column that gives an indication of the condition of the intima. (2) the light streak which gives an idea of the tunica media. (3) the arterio-venous crossings and (4) any pathological perivascular sheathing which may take place when fibrosis of the vessel wall sets in in the later stages of the disease. (5) Finally he looks at the disc and the eye-grounds for any œdema, hæmorrhages and exudates.

To understand the changes taking place in the retinal vessels let us briefly consider the present day conception of the pathological sequence of events taking place in the kidney arterioles. We know that hypertension is due to a peripheral resistance to the blood flow and in order to overcome this resistance and maintain an adequate circulation through the kidney glomeruli there is *spasm* of the renal arterioles, followed by work hypertrophy of their tunica media. This change over a long time will produce more permanent changes—*hyalinization and lipoid infiltration* of the vessel-wall and later *interstitial fibrosis* between the hypertrophied muscle bundles. This causes an increase in the total diameter of the vessel but a narrowing of the lumen. Finally degenerative changes of a *diffuse hyperplastic-sclerotic* nature involve the subintimal connective tissue. This causes a gradual blocking of the glomeruli. It has been proved experimentally, and also assumed to be taking place in man, that diminution of the blood flow through the glomeruli releases a pressor substance of a chemical nature that further increases the blood-pressure, which acts independently of the central nervous control. In order to maintain this further increase of blood-pressure caused by the liberation of this pressor substance the blood vessels will have to undergo still further hypertrophy which will result in still further narrowing of the lumen and still further diminution of the blood-flow through the glomeruli. A *vicious circle* is thus established. In the closing stages hyaline necrosis of the arterioles—the stage of *necrotizing arteriolitis,* takes place. In this stage there is retention of nitrogenous waste products due to failure of kidney function, and the closing chapter is written under the head of malignant hypertension and nephrosclerosis.

The sequence of changes that take place in the retinal arterioles is exactly the same as what we saw taking place in the kidney arterioles, *viz.*: 1. Angiospasm. 2. Work hypertrophy of the tunica media. 3.

Interstitial fibrosis in the tunica media. 4. Diffuse hyperplastic sclerosis affecting the intima and 5. Necrotizing arteriolitis.

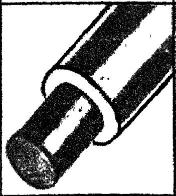
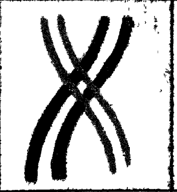
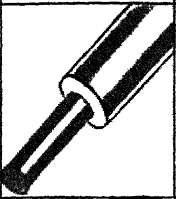
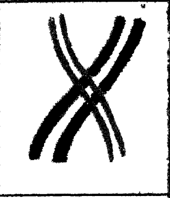
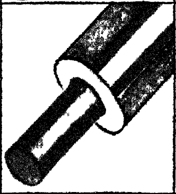
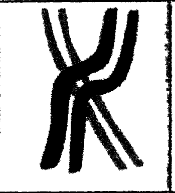
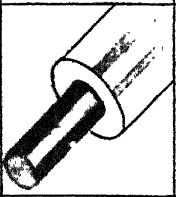
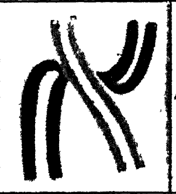
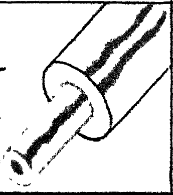
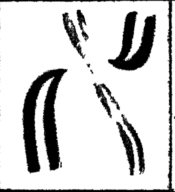
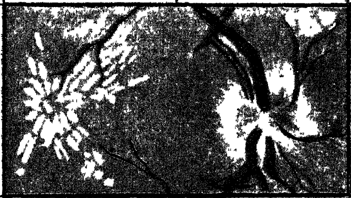
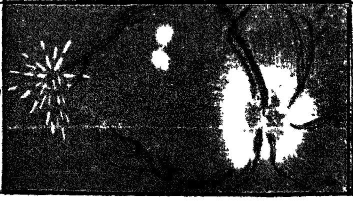
Therefore a critical study of the retinal arterioles will at once give an idea of the corresponding changes in the arterioles all over the body, and particularly in the kidney arterioles.

In the *initial stage,* let us call it the preorganic phase, angiospasm is evidenced clinically by ophthalmoscopic changes long before evidence of renal involvement. Nowhere can vasospasm be better seen than in the eyegrounds in hypertensive subjects. There is generalised arteriolar spasm without irregularity of lumen. There is no change in the light streak and no change at arteriovenous crossings. Ordinarily there is a ratio of 3 : 5 between the thicknesses of the walls of a retinal artery and vein. If arteriolar spasm causes that ratio to alter to 2.5 : 5 it is surprising that that little change can be appreciated by the ophthalmoscope. These changes are functional and disappear and reappear in the same retinal branch or a different one.

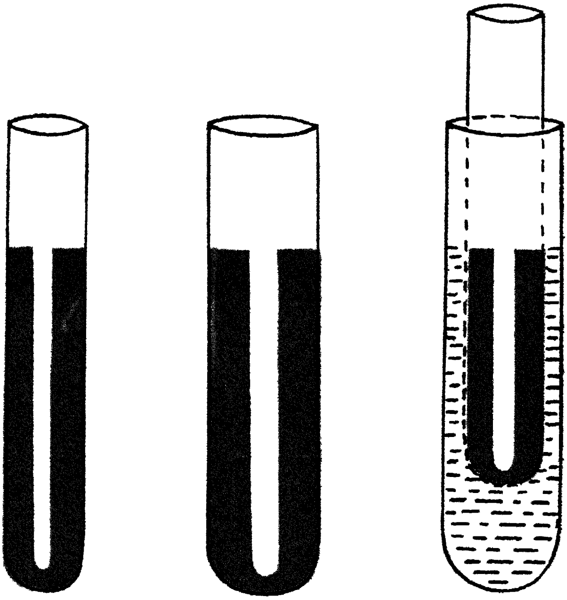
In the *second stage* with work hypertrophy of the tunica media more permanent changes take place. The thinning of the blood column remains permanent. The "glassy" hypertrophy of the media causes broadening and brightening of the light streak, a change known as "copper-wiring" of the retinal arteries and arterioles. At the arteriovenous crossings evidence of thickening and hardening of the arterioles is seen in the compression of the vein that takes place. If the vein crosses over an artery a peculiar arching effect is seen (Plate group II B.) and where a vein is seen passing underneath an artery it shows compression. (Plate II group II B). Because of this the distal part of the vein becomes more engorged—an effect called" banking" of the venous blood.

When actual lipoid infiltration of hyalinized media takes place the vessel begins to lose its transparency so that the blood column appears paler and at the arterio-venous crossings we find the portion of the vein behind the opaque artery invisible, incidentally showing the amount of thickening of the vessel-wall, in proportion to the lumen of the arterioles. When interstitial fibrosis begins it brings about a shortening of the vessels in their long axis, the effect of which is seen at the arterio-venous crossings. Since at these crossings the artery and vein are bound together by a common adventitia the vein will be hitched up. (Plate II group II B). In later stages the fibrotic change makes the vessel wall so opaque that white lines will be seen running by the side of the blood column. This is called "silver wiring" of the arteries. The blood column in the arterioles will also appear paler. (Plate II group II & III).

With the advent of the *third stage* the stage of diffuse hyperplastic sclerosis, changes begin to take place in the intima and are shown by the irregularities in the lumen in addition to generalized arteriolar constriction. The irregularity of the lumen is due to a proliferation of the

	ARTERIOLES AND CHANGES IN THE LIGHT STREAK	ANTERIO-VENOUS CROSSINGS	CARDIO-VASCULAR-RENAL CHANGES	MORTALITY IN FOUR YEAR PERIOD
NORMAL				
GROUP I VASO-SPASM			B.P. 150/90 HEART: NORMAL KIDNEY: SATSF.	10% CEREBRAL OR CORONARY ACCIDENTAL THROMBOSIS
GROUP II A HYALINIZATION OF TUNICA MEDIA			B.P. 180/110 HEART: HYPERTROPHY + KIDNEY: SATISF. LIBERATION OF PRESSOR SUBST.	30% CEREBRAL OR CORONARY ACCIDENTAL THROMBOSIS
GROUP II B INTERSTITIAL FIBROSIS OF TUNICA MEDIA			B.P. 190/115 HEART: HYPERTROPHY + + KIDNEY: SATISF. VICIOUS CIRCLE BEGINS	30% CEREBRAL OR CORONARY THROMBOSIS
GROUP III DIFFUSE HYPERPLASTIC SCLEROSIS OF TUNICA INTIMA			B.P. 200/120 HEART: IMPAIRED KIDNEY ALB. + IN URINE	60% CEREBRAL OR CORONARY THROMBOSIS
GROUP IV A MALIGNANT HYPERTENSION SCLEROTIC TYPE			B.P. 240/140 HEART: IMPAIRED KIDNEY: ALB. +++ BLOOD CASTS IN URINE	90% KIDNEY FAILURE
GROUP IV B MALIGNANT HYPERTENSION ANGIOSPASTIC TYPE			B.P. 250/160 HEART: IMPAIRED KIDNEY: ALB. +++	57% KIDNEY FAILURE

R.D. NAYAK.



subintimal connective tissue. This proliferation is uniform round the lumen as evinced by an uniform narrowing of the blood column. It may not however be continuous through the whole length of the vessel. This is in contrast to another type of narrowing that takes place in senile athero-sclerosis. In the latter the change is to be found not in the arterioles but in the central retinal artery or its first divisions. The atheromatous plaque here is eccentric and so causes narrowing of the lumen from one side, and is liable to favour an embolism of the central retinal artery or one of its first divisions. It takes little contributing part in the general arteriolar sclerosis seen in hypertensive vascular disease, although the two may be associated.

Going back to the third stage of hypertension, at the arterio-venous crossings one sees the compression of the vessels well marked and there is evidence of a sclerotic change spreading into the venule at the point of crossing, both up and down the stream, thus considerably narrowing the lumen of the vein. An occlusion is iminent, but even if it does take place endothelial canalisation through the obstruction and formation of collateral channels lead to a reestablishment of the flow. At this stage therefore hæmorrhages into the retina due to a branch thrombosis are not uncommon but not necessarily of grave prognostication, because it is just an ocular counterpart of a cerebral or coronary vascular accident to which the patient may succumb at this stage.

The curtain is now closing in and we come to the *last stage*—the stage of malignant hypertension. A dramatic change in the retinal picture takes place. It corresponds with the stage of arteriolar necrosis and retention of nitrogenous waste products due to failing kidneys. The general theme of the picture is one of retinal œdema, "cotton-wool" type of exudates, hæmorrhages and a "star-figure" at the macula resulting from a collection of serous exudate, remains of hæmorrhages and accumulation of retinal œdema fluid round the macula Sometimes the serous exudate is in such abundance that it causes a detachment of the retina. With extensive tissue destruction the lipoidal debris accumulates round the retinal veins seen ophthalmoscopically as white streaks along the veins. If the patient survives, optic atrophy of an inflammatory type follows. There is no escape from death which comes earlier in the younger subjects, and may be delayed as long as even eight years in the old.

The changes so far described are as taking place in a case of progressive hypertensive vascular disease, indicating the capacity of the subject to react to this rise of vascular tension, given time to do so.

However there is another type of hypertension which sets in precipitiously, and rapidly runs into the maliganant stage. A typical picture would be presented in the case of hypertensive retinopathy in pregnancy. The vascular changes are of so precipitous and rapid a nature that the subject hardly gets a chance to react by structural sclerotic changes in the vessel walls to resist the onslaught of hypertension. Naturally such a subject will react by spastic changes of a severe type, with a direct stepping into Group IV B, angiospastic retinopathy, without going through the pictures of Group II and III. The retinæ of such cases when seen with an ophthalmoscope will present a picture of malignant hypertensive retinopathy but with spastic changes in the vessels and not sclerotic changes. Such cases naturally carry a very serious prognosis, but with successful termination of pregnancy or the removal of any other probable cause *e.g.* a "surgical" kidney, the condition rapidly improves, the retinal œdematous changes subside, and the vision is restored.

Yet another type of kidney lesion has to be considered. In chronic glomerulo-nephritis due to a chronic glomerulitis in which the tubules also share the inflammation, the glomerulotubular unit is destroyed and is replaced by an increase in the interstitial tissue of the kidney which reduces the vascular tree of the kidney from a full-bloom to one resembling a withered tree with only a few base branches. The kidney-function suffers in the same way as in nephrosclerosis, with the liberation of the pressor substance and the establishment of a vicious circle as explained above, so that the terminal retinal picture will necessarily be similar to the one in nephrosclerosis. The ophthalmoscopic picture will differ in that (1) the vasospastic changes will be more marked than sclerotic changes; (2) there will be a characteristic pallor of the whole fundus reflective of the progressive anæmia in these cases.

Reviewing our findings we gather that,

1. Angiospastic changes denote progressive activity,
2. Sclerotic changes denote chronicity.
3. If the angiospastic state changes into the sclerotic condition it denotes the ability of the individual to resist the spastic features of hypertension.
4. Retinitis, means serious prognosis.
5. Oedema of the optic disc and retina ring the death-knell of the patient and are signs of fatal prognosis.
6. Malignant hypertensive retinopathy with vasospastic changes (*i.e.* without sclerotic change) denotes a precipitous onset of the disease and a grave prognosis. However it is reversible if the cause is found and treated.
7. Similar changes supervening on sclerotic vascular changes means a failure of the kidneys and the terminal stage of the disease.

How and how much can the ophthalmologist aid the physician by applying this knowledge ?

1. He is the first to spot early changes of an angio-spastic nature.
2. He can trace the pathological sequence of events and place a

given case in one of the groups and pronounce a prognosis by observing whether there is only vascular spasm as in Group I, hypertrophy of tunica media as in Group II, arteriolar sclerosis involving the intima as in Group III, or malignant retinopathy as in Group IV.

3. He can distinguish a case of malignant hypertension of precipitous onset, from one in which it has supervened on a previously damaged arteriolar bed. The former though more malignant can improve or subside without residual vascular damage. But if it persists or is superimposed on sclerotic retinal changes the prognosis is very grave.
4. He can distinguish between
   (*a*) a case of hypertensive vascular-disease.
   (*b*) a senile atheromatous condition and
   (*c*) the closing stage of chronic glomerular nephritis, with its characteristic pallor of the fundus.
5. In the hypertension of pregnancy he is in a position to dictate the termination of pregnancy, when he sees.
   (*a*) Vasospasm in the *pre-eclamptic* stage, or
   (*b*) in the *eclamptic stage* does not see the disappearance of vasospasm after the termination of the convulsive phase.

This is advised to prevent maternal mortality and to prevent development of cardio-vascular disease in the mother subsequently.

6. In hypertension due to a "surgical" kidney, he can say which is the kidney likely affected because the retinal changes will usually be more marked on the affected side.

But the help ends here. The limitations of the ophthalmologist are:

(1) He cannot say what particular type of nephritic condition contributive to hypertension is present-whether infective, degenerative, senile or secondary to fibrosis, so long as all of them casuse renal ischaemia, causing rise of vascular tension and renal failure.
(2) He cannot say what particular part of the kidney is damaged and the extent of the damage.

To sum up the importance of ophthalmoscopy in essential hypertension in one sentence one can say that the ophthalmoscope is just as valuable an instrument in the study of the patient with hypertension and eclampsia, as renal function tests or the sphygmomanometer.

BOOK REVIEW

A Text Book of Bacteriology by Professor N. G. Pandalai, M.D., D.T.M., F.R.C.P. (Edin.) Professor of Bacteriology, Andhra Medical College, Vizagapatam, pp. 748. The Bangalore Printing and Publishing Co., Ltd., Mysore Road, Bangalore City, Price Rs. 18/-.

This Text Book of Bacteriology appears as an attractive cloth bound volume. The printing is generally good. The subject matter has been presented in a clear manner. The text makes easy reading. An index of 24 pages is well compiled and affords easy approach to the text.

The 31 corrigenda printed at the end of the book are unfortunate. Some printing errors are still noticeable.

The omission of illustrations having been mentioned by the author himself in the preface, need not be discussed further.

If it is admitted that it is necessary to curtail the reading matter, some method will have to be devised. Instead of going into detailed suggestions it may be mentioned that portions of the text in several chapters could either be put in small type, if not deleted, without a serious loss to the scientific dignity and utility of the book for undergraduates.

The book in its present form may satisfy the less ambitious postgraduate in Bacteriology, but is a bit too large for the undergraduate.

It may be added that very careful attention must be paid to the rules of the language by authors proposing to write medical books in the English language. The book under review unfortunately contains a few mistakes.

A word to the Printers and Publishers :—At a time when medical books are likely to appear in India the Printers and Publishers should help the authors in the production by adopting newer methods of printing, illustrating, etc., and being reasonable in charging costs of preparation and publication.

As a book containing much valuable information written in simple English, the text book by Professor Pandalai is to be welcomed. A student will find in this book useful material for his study, if he is not scared by the large size and the high price.

P. V. Gharpure.

CURRENT MEDICAL LITERATURE

MEDICINE

THIOARSENITES IN AMEBIASIS. Anderson H. H., Johnstone H. G., Gostick W. Chevarria A. P., Packer H., J.A.M.A. 140: 1251-56, 1949. 5 Tables, 21 References.

The authors after reviewing the literature in the treatment of amœbiasis put forward a plea that there is no satisfactory amœbicidal drug. They have tried two new drugs called Thioarsenites in which there is substitution of—SH groups for oxygen in carbarsone oxide. These two derivatives are called dithiocarboxymethyl and dithiocarboxyphenyl. These two drugs have some anti-amebic activity with a reduced toxicity for host's tissues. These drugs have been tested as regards their toxicity in various animals and found to be not toxic.

> "Of 82 patients, 77 with E. histolytica, 3 with Dientameba fragilis and 2 with Balantidium coli, 74 were cleared of their parasites over a four month follow-up period. Eighteen others, infected with Dientameba fragilis (2), Strongyloides stercoralis (12), Fasciola hepathica (1), Leishmania tropica (2) and Treponema pertenue (3) had no significant benefit following thioarsenite therapy. Complete clinical appraisal before, during and after therapy, including tests of urine, blood and hepatic, renal and heart functions, revealed no drug toxicity due to the dose levels employed (3.0 Gm. orally in ten days to 7.2 Gm. in twenty-four days). In addition, 13 of these patients with acute dysentery also received dithiocorboxyphenyl in retention enemas (3.0 to 6.6 Gm. in six days) with benefit and without evidence of drug toxicity to mucous membranes of the lower bowel as revealed by proctoscopic examination. No cutaneous reaction or damage to other tissues was observed. Twelve patients exhibited nausea or vomiting after 200 mg. doses of either thioarsenite. Coating of the tablets with phenyl salicylate permitted completion of therapy in all but 1 of these patients."

The authors come to the conclusion on the basis of laboratory and clinical trials that the detoxication of carbarsone oxide by substituted sulfhydril is an active agent when amebic invasion occurs in the various tissues of the body.

J. C. PATEL.

A VENOUS SHUNT FOR ADVANCED MITRAL STENOSIS, by BLAND E. F., SWEET R. H. J.A.M.A. **140**: 1259-65, 1949. 10 Figures, 17 References.

In mitral stenosis acute left sided failure occurs due to dilatation of left auricle. Symptoms resemble that of left ventricular failure, even though the musculature of the heart is perfectly normal. In such cases digitalis, mercurial diuretics and low salt diet do not help. Symptoms clear with xygen therapy and rest in bed. This condition is entirely due to increased pressure in the left auricle. Authors have tried to relieve this pressure by performing anastomois between the dorsal segment branch of inferior pulmonary vein with azygos vien. They have operated upon 5 cases of mitral stenosis. Two had several such attacks of left auricular failure showing the symptoms of recurring pulmonary œdema. Operation was done on 5 cases, 4 females and 1 male, out of which 1 died on the 11th post-operative day. 3 cases have been followed up for a period of 12, 5 and 4 months respectively with remarkable success. One of them stood repeated operation of dilatation and curretage following pregnancy without any ill effects. No murmur due to the shunt was audible on the chest. Authors have given all details of the operative technique and consider the present report as preliminary and advocate further study of technique and results before final appraisal of results.

J. C. PATEL

OBSERVATIONS ON THE EFFECT OF AN ANIMAL PROTEIN FACTOR CONCENTRATE ON PERSONS WITH THE MACROCYTIC ANÆMIA OF PERNICIOUS ANÆMIA, OF NUTRITIONAL MACTOCYTIC ANÆMIA AND OF SPRUE, AND ON PERSONS WITH NUTRITIONAL GLOSITIS. SPIES T. D., LOPEZ G. G., MILANES F., STONE R. E., TOCA R. L., ARAMBURU T. AND KARTUS S. Blood, The Journal of Hematology, IV 819-826. 4 Figures, 18 References.

Authors have traced the history of hatchability of eggs since many years. They produce evidence from the latest published work that some animal factor present in animal food was necessary for proper hatching of the eggs, the hatchability, growth and viability of chicks. Lederle laboratories have produced an animal protein factor concentrate by the growth of bacteria and consider that this is identical or nearly related to Vitamin B12. This animal factor was given a clinical trial in 5 cases of pernicious anæmia, 4 cases of nutritional macrocytic anæmia, 3 cases of nutritional glossitis and 3 cases of tropical sprue. The dose employed was a total of 5 cc. in a period of 2-3 days to 5 cc. daily for 14 days. The details of these cases along with the figures are given in the paper. In all cases there was a positive hæmatological response and improvement in nutritional glossitis unassociated with anæmia.

J. C. PATEL.

PERNICIOUS ANÆMIA AND RELATED ANÆMIAS TREATED WITH VITAMIN B12. JONES E., DARBY W. J., AND TOTTER, J. R. Blood, The Journal of Hematology, IV, 827-844. 26 References, 3 Tables, 2 Figures and 12 Charts.

Authors review the published literature on the treatment of pernicious anæmia with Vitamin B12, and report observation on 8 patients with pernicious anæmia, 1 with sprue, 1 with nutritional macrocytic anæmia and 1 with anæmia secondary to the absorptive defect of intestinal lipodystrophy. They were treated with Crystalline B12. In the series they were unable to obtain a satisfactory erythrocyte level from a single injection of 50 to 75 micrograms of Vitamin B12. They consider one microgram per day as the rate of utilisation of Vitamin B12 in pernicious anæmia, but they are of the opinion that it would be better to allow 2 or 3 micrograms per day for a patient of pernicious anæmia for adequate and maximum rate of hæmopœsis. In this series and from published case reports from other authors, they emphasise the unreliability of reticulocyte count as a quantitative measure of activity of a substance or of the adequacy of therapy in a given patient. They saturated one patient with large doses of Folic Acid and carried out the excretion test of Folic Acid in a number of patients following administration of Vitamin B12. From the results they consider that Vitamin B12 administration has no effect on urinary excretion of Folic Acid in six cases of pernicious anæmia and one case of sprue.

J. C. PATEL.

NEEDLE BIOPSY OF THE LIVER. R. C. COGSWELL, L. SCHIFF, S. A. SAFDI, D. F. RICHFIELD, C. W. KUMPE AND E. A. CALL. J.A.M.A. 140: 385-390, May, 1949.

Dr. Schiff describes his experience of 400 liver biopsies in 345 patients. It is a safe and useful procedure. The cases for liver biopsies should be carefully selected. Indications for the biopsy are many. It may be performed in any case of liver disease for diagnosis where biochemical tests give equivocal results. It may also be employed for confirmation of diagnosis for study of progress of any case for evaluating any of the therapeutic measures employed and even in diagnosis of certain systemic diseases. It should not be performed if the patient is not co-operative, if the blood prothrombin level is low, if there is infection of the lower lobe of lung or light pleural space, and if there is chronic passive congestion of the liver.

If there is ascites it should be evacuated before the liver biopsy is attempted. Complications that are likely to occur are local pain epigastric discomfort, perihepatitis,-intra abdominal or intrapleural hæmorrhage, pneumothorax and severe apprehension in a neurotic patient. The danger of hæmorrhage is not very great. In 15% of cases the liver biopsy helped to correct the clinical misconceptions, while in 4% of cases it gave results not consistent with the actual disease. Inconsistensies occured in cases of focal lesions of liver.

B. B. YODH.

AUREOMYCIN IN PRIMARY ATYPICAL PNEUMONIA. G. MEIKLEJOHN-CAPT. R. J. SHRAGG. J.A.M.A. 140: 391-397, May, 1949.

The clinical course of primary atypical pneumonia is very variable and it is difficult to assess the value of any therapeutic measure in this disease. So in this series of 38 cases, 18 cases in which the clinical picture with blood count and X-Ray was unequivocal and the temperature was 102° F or more, were treated with aureomycin and the rest of 20 cases with equivocal evidence of primary atypical pneu monia were given penicillin and then the results were compared. Aureomycin was given in doses of 1 gm. orally every six hours with initial 50 mgm. intravenously. This gave blood level of 0.125 to 10 micrograms per 100 cc. with wide individual variation. Toxic reactions of nausea and vomiting occured in 50% of cases. Penicillin was given in doses of 100,000 units every six hours.

In aureomycin group $\frac{2}{3}$ patients temperature touched normal in 2 days and all were afebrile after five days of treatment. In penicillin group $\frac{1}{3}$ of cases temperature came down to normal in 2 days and the rest followed a variable course, and four cases became actually worst. The course of disease with penicillin treatment is the same as in untreated cases. With aureomycin the response was universal and fairly rapid. Three cases relapsed after cessation of aureomycin therapy but responded immediately on reinstitution of the aureomycin.

The titre of cold agglutination test was higher in patients in whom the fever continued longer and hence they were high in penicillin series.

B. B. YODH.

INSULIN FAT ATROPHY. OESTREICHER AND WATSON. Am. Jr. Med. Sci. 218: 172-178, Aug., 1949.

The irregular disappearance of the subcutaneous fat in some diabetics who receive insulin is a disturbing and as yet unexplained phenomenon. This type of disfigurement has been noted in about 30% of patients treated with insulin.

Various theories have been propounded to explain insulin fat atrophy. The acid reaction of crystalline insulin (pH 3.0) has been suggested, but is not likely as protamine zinc insulin which also causes atrophy has a pH of 7.3. Lipolytic enzymes in insulin have been blamed but not demonstrated. Tricresol used as a preservative in commercial insulin has been suggested but experiments with aqua cresylata were negative. Repeated trauma is unlikely as atrophy does not occur in narcotic addicts who inject themselves.

The authors conducted a series of experiments on rats rendered diabetic with alloxan and drew the following conclusions: 1. Fat atrophy does not occur at the sites of the repeated injection of insulin in rats rendered diabetic with alloxan. 2. Pure zinc insulinate had no effect upon lipase activity in vitro at the concentrations employed. 3. Tricresol depressed the activity of lipase *in vitro* and therefore may be of etiological importance with respect to insulin fat atrophy.

The circumstances responsible for the development of insulin lipodystrophy pose a series of baffling questions. For example, why does the condition affect only one out of about every three persons who use insulin? Why does it occur in young people of both sexes, but among adults practically only in women? Why do some diabetics exhibit atrophy and others hypertrophy of the subcutaneous fat. The answers to these are elusive. Despite the lack of direct evidence the possibility that tricresol, or some other constituent of commercial insulin, may play a part should be entertained.

The only available preventive measure is to vary the site of injections and to use highly concentrated preparations of insulin.

E. J. BORGES.

SURGERY

DRAINAGE OF THE BLADDER WITH SPECIAL REFERENCE TO URETHROSTOMY. BY JOHN SANDRY. Postgraduate Medical Journal, 25 : 71-77, 1949, 17 References.

Efficient drainage is still to be regarded as the first line of defence against the three serious complications which may follow any operation of the bladder, namely hæmorrhage, infection and urinary extravasation.

One of the main problems facing the surgeon who carried out immediate closure of the bladder after prostatectomy is that of satisfactory bladder drainage. Post-operative extravasation of urine is the most important local cause of mortality and morbidity of "closed" operations and unless it is eliminated, there is a real danger that this method will, in the long run, prove to be a step backwards in prostatic surgery.

The method of bladder drainage may be conveniently grouped under three headings; firstly drainage of the obstructed bladder, secondly drainage of the paralysed bladder and thirdly post-operative drainage. In the first and second groups temporary or permanent drainage may be required.

Methods of bladder drainage to be considered are :

(A) *Perineal drainage of the bladder.*—This is a method now only used to any great extent by the perineal prostatectomist. From the anatomical point of view it is the ideal method, as drainage is directly downhill. Unfortunately its practical value is limited by possible damage to the perineal muscles and nerves and by pressure of the tube and late scarring in and around the wound, resulting in incontinence or formidable stricture.

(B) *Suprapubic drainage.*—This has three advantages over other methods. The absence of any foreign body in the urethra eliminates genital infection ; urine can be collected by various types of apparatus while the patient is ambulant and thirdly, such drainage can be maintained indefinitely. Unfortunately the defects of suprapubic drainage are only too apparent. These are :

(1) Leakage of urine around the tube with its physical and mental discomforts.

(2) Danger of damage to the peritoneum in the blind leak-proof methods.

(3) The most serious mechanical defect is that any suprapubic drainage is always drainage uphill and that the bladder always contains residual urine.

(4) That in those poor risk cases where radical surgery is contra-indicated the mortality rate attributable to the operation is anywhere up to 30%.

(C) *Catheter drainage,* though simple and convenient, has one important limiting factor, namely urethritis. This gives rise to a foreign body reaction in the urethra with an increased mucoid secretion which after two or three days becomes frankly purulent. Provided the urethra and the external meatus are large, no serious effects may occur. But interference to free drainage around the catheter may occur due to a small-sized urethra, a small external meatus or to an œdema of a normal sized meatus. Back pressure due to these causes may lead to blockage of Littres glands, periurethral suppuration, meatal stricture, vesiculitis, cystitis, etc. There is a very wide variation in the size of the urethra and external meatus. On investigation it was found that only about 8% of cases, as judged by the size of the urethra and the external meatus, are found suitable for drainage for seven days or more, even when œdema of the external meatus does not occur.

(D) *Urethrostomy drainage of the bladder.*

(*a*) Dissatisfaction with routine methods of bladder drainage has lead the author in two years to employ urethrostomy in nearly 400 personal cases. The mortality rate in poor risk cases has been reduced thereby to less than three per cent, none of which were due to an upward spread of urinary infection. Urethrostomy may be performed by the open or closed method. The closed method is suitable for the majority of cases.

(*b*) In the closed method, a rubber catheter is passed along the urethra to its full length and the distal end securely clamped with a curved artery forceps. The forceps is advanced until its beak reaches the bulbous urethra and by rotating the handle through 180°, the point is made to present in the perineum where it is cut down upon. The end of the catheter is disengaged from the forceps and is drawn through the incision to the correct length for bladder drainage. This method is rapid, simple and requires no special equipment. In seriously ill patients it can readily be performed in bed under local anæsthesia. In that group of cases, comprising about 20%, where the external meatus is stenosed or the urethra congenitally small, the "open" method has been employed. An incision is made in the perineum on the curve of a small metal bougie. The edges of the urethral mucosa must be carefully identified and grasped with fine tissue forceps before attempting to pass the catheter, otherwise the urethra will tend to invaginate and prevent the passage of the instrument. The open method is much more difficult than the closed method of urethrostomy, as it requires wider dissection in a vascular area. It should not be attempted under loca anæsthesia.

The best position for the urethrostomy opening has been found to be in the scrotal raphe about one inch in front of the perineo-scrotal angle. The site of this opening is a matter of importance. If placed too far back, it is less accessible for nursing, contamination from the anus is more likely, kinking of the tube by the weight of the scrotal contents is hard to avoid, and spontaneous closure of the fistula after removal of the catheter is slower. If too far forward, the catheter tends to kink excessively at the subpubic angle and if it should come out, replacement may be difficult.

(*c*) Fixation of the catheter is secured by several half hitches of non-absorbable suture to the skin in front or by using a 22-26 Charriere whistle tip or a Foley catheter.

Disadvantages of urethrostomy are:

(1) A scrotal hæmatoma may form which is not of much moment.

(2) Replacement of the catheter may be difficult, especially if delayed for more than a few hours.

(3) Slight incontinence of urine sometimes occurs, but normal control always returns after a few weeks.

(4) Lastly, leakage of urine occurs with each micturation after removal of the catheter. This is of course anyway under voluntary control and ceases in 4-5 days in the average case, and always within a day or two

of the patient becoming ambulatory. In all cases healing has been spontaneous.

(*d*) Leakage is undoubtedly the chief disadvantage of urethrostomy drainage but it is, after all, a small price to pay for the added safety the method confers on "closed" operations of the bladder. Unlike the leakage associated with suprapubic cystostomy it is, however, under voluntary control.

To summarise the advantages of urethrostomy:

(1) Compared with suprapubic cystostomy, there is the simplicy of procedure.
(2) The difference between dependent and uphill drainage and
(3) in bladder obstructions, there is the striking difference of the mortality rates of the two methods.
(4) Post-operative drainage is secured away from the suture line and allows complete closure of the bladder in most cases.

Compared with catheter drainage most of the ill effects of urethritis are avoided by excluding ⅔ of the urethra and there is always adequate room for free urethral drainage alongside the catheter.

While it can be said that a stricture will almost invariably follow incision of the penile urethra, it can be stated equally dogmatically that this never occurs in the perineal urethra unless the entire circumference has been divided and the ends separated.

Urethrostomy drainage, though not ideal by any means, goes a long way towards solving many of the defects of other methods. When bladder drainage is required pre-operatively, urethrostomy has the great advantage of mechanical efficiency, simplicity and added safety over other methods. As an alternative to immediate prostatectomy, particularly in the "poor" risk cases with extra-urinary complications, urethrostomy will, it is held, be found to yield the best results. Post-operatively it confers an increased margin of safety on complete closure after operations on the bladder or the prostate. Furthermore drainage can be maintained indefinitely in order to ensure sound healing of the abdominal wound.

K. BOND.

RECURRENCE RATE OF HERNIA IN CONNECTION WITH BRIEF CONFINEMENT TO BED FOLLOWING HERNIOPLASTY. ANDERS WENCKERT, ACTA CHIR. Scandinav. 98 : 205-211, 1949.

The authors have studied a comparative series of cases to determine whether the modern tendency to make patients get out of bed early after operation has any effect on the recurrence rate after a hernioplasty. They were very careful to use case records that were comparable in most respects so that differences of factors did not vitiate the conclusions drawn.

In 331 cases operated on between 1937 and 1942 the average period in bed after operation was 11 ± 3.5 days. They were all followed up by answers to questionaire over 2 years. The recurrence rate was 10.3 per cent. In 295 cases operated on in 1943 to 1945 the average stay in bed was 3 ± 0.8 days. Followed up for over 2 years by questionaire the recurrence rate was 10 per cent.

The study indicates that early ambulation had no effect on the rate of recurrence of inguinal hernia after hernioplasty.

E. J. BORGES.

BILATERAL MAMMARY CARCINOMA IN THE MALE COINCIDENT WITH PROLONGED STILBOESTROL THERAPY. HOWARD AND GROSJEAN. Surgery. 25 : 300-303, Feb. 1949.

Tke authors present a case report of a patient who received stilbœstrol therapy for carcinoma of the prostate with bone metastases for almost 5 years. A total of

40,280 mg. of diethylstilboestrol was taken by the patient over this period. At the time of his death in January, 1948 the patient had developed bilateral scirrhus carcinoma of the breast.

E. J. BORGES.

TREATMENT OF GONORRHEAL ARTHRITIS WITH PENICILLIN. SPITZER AND STEINBROCKER, New York. Am. Jr. Med. Sci. 218 : 138-144, 1949.

This report is an evaluation of the effectiveness of penicillin in gonoccal arthritis. It summarises the experience in their wards for the past 3 years.

Twenty-eight cases received penicillin as the basic treatment as soon as the diagnosis was made. Of these 23 were considered cured or greatly improved and 5 were failures. The cured cases had completely restored joints. The greatly improved cases had subsidence of all symptoms and the residual joint improvement consisted of only slight limitation of movement or slight tenderness. As compared with pre-penicillin days the results were remarkable. Keefer reported 26 cases treated by immobilisation and general measures; of these 18 were cured, 4 had residual stiffness and 4 had ankylosis. In another group of 44 patients treated by aspiration, open lavage for purulent effusions, only 17 showed complete joint recovery.

The advent of the antibiotics probably requires a revision of the methods of management of these infections. The principles of rest and immobilisation of infected joints, sometimes for long periods, to assure fixation in optimum positions served their purpose when specific infections frequently and inevitably threatened serious articular damage and an ankylosed joint. When arthritis is due to an organism susceptible to antibiotics, the older methods probably must be modified now for the best results. More attention must be given to the judicious use of physical therapy and exercise in increasing amounts as soon as the infection is under control and within the range of the patients tolerance. The adequate use of posterior resting splints, rather than prolonged immobilisation, seems more suitable.

E. J. BORGES.

ACUTE MASTITIS. ANTHONY WALSH. Lancet. 2 : 635-638, October, 1949.

The author records his experience of acute inflammations of the breast and advocates certain departures from generally accepted practice in the management of these cases.

In a series of 96 cases of acute mastitis without abscess formation the treatment consisted of intramuscular injection of 20,000 units of penicillin every 4 hours until the inflammation had completely resolved. The author advises against weaning the infant. In 88 cases of the 96 the lactation was not suppressed, but free flow of milk from the affected breast was encouraged by the patient expressing the milk out with her fingers at feed times after the baby had been fed at the opposite breast. In 74 of the 88 cases the milk so expressed from the affected breast was boiled for 5 minutes and fed to the infant. In no case was there any illeffect on the baby or the mother, and the child was carried through the lactation period as usual.

When an abscess has formed the condition requires early drainage as penicillin has no effect once suppuration has occurred. It is therefore important to recognise the presence of pus. To wait for fluctuation in many cases is waiting too long. Any tense and very tender mass in an acutely inflamed breast probably has pus and should be incised. This gives immediate relief from pain. As regards incision the author is not in favour of the text-book radial incision as it often leaves an ugly scar. He advocates an incision along the periphery of the areola through the skin and subcutaneous tissue only, and insertion of an artery forceps into the absces cavity. The breast is then palpated against the point of the artery forceps and indurated loculi of abscess are opened into the main cavity. The results by this method have been excellent, in none of the 31 cases so treated did a secondary abscess form.

E. J. Borges.

PEDIATRICS

"Idiopathic Renal Acidosis in an Infant with Excessive Loss of Bicarbonate in the Urine." By : Thomas Stapleton. The Lancet : 683-685, 1949, Tables 2. Fig. 1. Ref. 13.

The author reports a case of a child which upto the age of 5 months was normal. She developed vomiting 3 to 5 times a day with severe constipation and stopped putting on weight in spite of normal diet. She was admitted in the hospital at the age of 10 months and investigated. Clinically she was dehydrated. The skin was loose and inelastic, and there was acidosis. Her respirations were deep. The plasma carbon-dioxide combining power was low. In spite of this, urine was constantly alkaline. The child failed to improve on infusion of whole blood, plasma and normal saline. She improved remarkably with infusion of 1/6th molar sodium lactate solution. The improvement was far in excess of the amount of fluid given and was evidently due to sodium lactate. The improvement was maintained and child was brought back to normal with large oral doses of sodium citrate. Treatment was then stopped but within three days the child was moribund. Reinstitution of sodium citrate quickly ameliorated the symptoms. All this time large amounts of bicarbonate were passed in the urine.

After nine weeks the citrate was discontinued and child remained normal. Apparently it was a functional disturbance of kidney which was unable to conserve the bicarbonate leading to acidosis.

Similar cases have been reported in the literature.

S. N. Shah.

Megaloblastic Anæmia in an Infant. By: J. H. Hutchison and P. MacArthur. The Lancet, 1 : 916-917, 1949. Fig. 3. References 9.

True Adissonian pernicious anæmia is very rare and macrocytic anæmia with megaloblastic bone marrow is also uncommon in infants and children. Probably some of the cases are missed because the bone marrow is not so often studied.

The authors describe one case of a child aged 1 year 5 months who had two attacks of gastro-enteritis, developed anæmia at the age of 1 year.which responded to polytherapy of Iron liver and vitamin C. The relapse occured at the age of 1 year 5 months. She had hyperchromic macrocytic anæmia. Bone marrow showed megaloblastic erythropoiesis. She had achlorhydria but it was not histamine fast.

She was given folic acid 10-20 mg. per day with very satisfactory results. It is possible that she developed deficiency of hæmopoietic factor due to gastro enteritis.

To day highly potent and specific hæmopocetic agents like folic acid Vitamin B12 intravenous iron etc. are available. They cannot be used properly without an exact diagnosis. The polyvalent blunderbuss treatment is often wasteful and ineffective. The exact diagnosis cannot be made without the study of bone marrow. Today the marrow study has become obligatory in adults but in children it is in its beginning because of difficulty in obtaining the bone marrow. The iliac crest puncture is easy at all ages and its marrow is as representative as sternal marrow.

The commonest causes of anæmia in childhood, infection and malnutrition, and can be easily diagnosed. The less common and often diagnostic problems are leukæmia, aplastic anæmia, macrocytic anæmia, hæmolytic anæmias, unrecognised cœliac disease etc. In all these cases bone marrow often gives a clue to diagnosis.

It is very difficult for a general physician to keep pace with all the advances in hæmatology and if special hæmotogical clinics are established in childrens hospitals they will be vast sources of further knowledge.

S. N. SHAH.

THE EARLY DIAGNOSIS OF RICKETS. GRAY J. D. AND CARTER F. S. Archives of Disease in Childhood, 24 : 189-194, (September) 1949. 4 Tables, 18 References.

Authors after reveiwing the methods of diagnosis of early rickets and bringing the evidence of the unreliability of clinical and radiological methods, go on to say that plasma-alkaline phosphatase is the only reliable means of detecting active and latent rickets. They have followed King-Armstrong method as it requires less blood as compared to that of Bodansky. They find 11-20 units as normal with an average of 17 for children between one month and three years of age, in 56 controls by King-Armstrong method. Over that age the average approximates to the figure for adults. The diagnostic titre in their opinion lay between 25 and 40 units.

J. C. PATEL.

ANAESTHESIOLOGY

CONCERNING SPINAL ANALGESIA. WILLIAM MUSHIN. Overseas Post. Grad. Med Jour. 3 : 177-182, January, 1949.

In this informative article the author explains many ill understood features of spinal analgesia.

There are two main methods of controlling the movement of the injected anæsthetic inside the subarchnoid space, namely, gravity, and volumetric displacement. The height to which an injection of light nupercaine will reach is determined mainly by the volume injected. The behaviour of heavy solutions is dependent on gravity and the curves of the spine. When a patient is lying on his back on a horizontal surface, two curves of the spine project posteriorly separated by the lumbo-acral projection : The thoracic curve with its greatest convexity opposite the 5th to 7th thoracic vertebræ, and the sacro-coccygeal curve. Two curves project forwards, the cervical, and the lumbo-sacral with its highest point opposite the 4th or 5th lumbar vertebræ. Thus, with the patient lying horizontally on his back a heavy solution when injected in the usual 3rd space tends to split up; most of it gravitates towards the mid-thoracic region, while some flows to the sacral region and is wasted. To prevent this the spine should be tilted slightly head down. The solution will not travel higher than the sixth or seventh dorsal segment and will give anasthesia upto the ensiform costilage.

Indications for spinal analgesia: 1. In very robust and burly individuals experience teaches that these are difficult subjects for general anæsthesia. 2. Where profound muscular relaxation is required ; here its supremacy is being challenged by curare.

Contra-indications for spinal analgesia :

1. Absence of perfect asepsis in the skin of the patient.

2. "Don't give a spinal to anyone you don't like the look of" *i.e.* any patient whose general health is likely to cause anxiety.

3. Beware of those who have an abdominal tumour of such a size that the diaphragm is pushed up and is unable to move efficiently. In these cases the danger lies in the fact that spinal analgesia paralyses most of the intercostals, and an embarassed diaphragm cannot maintain adequate respiration. The hitherto unexplained, and unpredicted deaths when spinal was used for Cæsarean section or for removal of large ovarian cysts were probably due to this cause. Spinal analgesia is only permissible in these cases if the patient is attended by an anæsthetist with the ability and the equipment to maintain oxygenation.

4. Beware of those with lung disease of such extent that they depend on every bit of their respiration for life. These do far better with general anæsthesia.

5. Beware of those with myocardial damage. The arterial flow through the coronary arteries is entirely dependent on the blood pressure and low blood pressure is a danger.

6. Think twice about patients with poor kidney function, *e.g.* long standing prostatic obstruction or hydronephrosis. Kidney secretion depends on a minimum of 80 mm. Hg blood pressure, and a patient on the verge of uræmia may ill afford to exist for one or more hours without kidney function.

E. J. BORGES.

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